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THE STATE OF THE VASOMOTOR APPARATUS IN PNEUMONIA[1]

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It has long been held that the toxines of pneumonia specifically injured the vasomotor cells.

This proposition we deny.

Earlier investigators, using the methods of their day, failed to show in this disease a normal change of blood pressure upon the stimulation of nerves afferent to the vasomotor centre. The present investigation, with more perfect methods, demonstrates a normal vasomotor reflex, with almost wholly consolidated lungs, in animals about to die.

METHODS

The animals used in this investigation were rabbits, cats, and dogs.

The organisms employed: The organisms used for infection were the pneumococcus Fränkel, for rabbits, and the streptococcus mucosus (also called pseudopneumococcus, pneumococcus mucosus) for rabbits, cats, and dogs.

[1] A preliminary account of some of these experiments was published in Boston Medical and Surgical Journal, 1914, clxx, pp. 125–216.

Our pneumococcus Fränkel, belonging to Dr. Cole's group II, was isolated originally by Dr. Rosenau and had been used by Dr. F. B. Grinnell to produce fatal septicaemia and pneumonia in rabbits. We received this organism in a state of high virulence. The stock culture was transferred about every third day to a fresh blood serum "slant." When an experiment was to be done upon a rabbit, a fresh transplant from the stock culture was made on blood serum or in plain beef bouillon (reaction against phenolphthalein + 0.6) and was incubated about 24 hours. From the blood serum culture the resultant surface growth was shaken up with 2 or 3 cc. normal saline solution (0.9 per cent NaCl) and the mixture was injected into the marginal ear vein. The growth in bouillon (1 to 2 cc.) was directly injected. The blood serum cultures were used on 7 rabbits from November 3 to November 15, 1913, and the bouillon cultures were used on 4 rabbits from November 17 to November 24. All these animals became very ill with pneumococcus septicaemia and four died in from 2 to 4 days after inoculation, showing that the virulence of the organism remained high during the series.

On February 20, 1914, a pure culture of the pneumococcus mucosus was obtained from the heart's blood of a man dead of pneumonia and control cultures were made from the lung. The pneumococcus mucosus produces a slimy growth on blood serum, has a well marked capsule, and is known to be very fatal. Cultures grown from the heart's blood were used on some rabbits and on all cats and dogs.

The procedure was as follows: A blood serum slant was inoculated from the stock culture and incubated 24 hours. A portion of the growth was washed into a syringe with about 0.5 cc. of normal saline solution (0.9 per cent NaCl) and injected into the peritoneal cavity of a mouse. Death followed in from 12 to 24 hours. A few minutes after death, several drops of heart's blood were placed in a flask containing about 40 cc. of fractionally sterilized "plain" beef broth (reaction + 0.6) and incubated. Broth to which glucose or other carbohydrate has been added permits a luxuriant growth, but the virulence is low. The

broth should not be sterilized in the autoclave but in the Arnold sterilizer; the high temperature of the autoclave changes the medium in such a way as to hinder growth. The cultures were used from 15 to 24 hours after incubation began. After 24 hours the culture begins to deteriorate. The virulence was tested by injecting into the peritoneal cavity of a mouse 0.001 cc., which caused death in 24 hours. Higher dilutions were not tried.

In dogs from 4.3 to 6.8 cc. of this culture per kilo were injected through a soft catheter passed down the trachea into a bronchus. In cats from 4.3 to 8 cc. per kilo were injected. In rabbits about 5 cc. per kilo.

The method was that used by Kinyoun and Rosenau,[2] who first produced experimental pneumonia in dogs. It has recently been employed by Lamar and Meltzer,[3] who, like their predecessors, used dogs only.

The measurement of the reflexes: The condition of the vasomotor centre was determined by measuring the reflex change in blood pressure produced by stimulating the depressor, the sciatic, and the central end of the vagus nerves. The carotid blood pressure was recorded by a membrane manometer which was calibrated against a mercury column at the close of each experiment. The mercury manometer was also used in a numbe for experiments. Ether was used as an anaesthetic, when necessary, but was given very cautiously, a few whiffs from time to time, in such a way as not to affect perceptibly the blood pressure during the observations. Ether was not given to animals so near death as to be wholly insensitive to the operative procedures. Curare was employed in those cases in which the vasomotor reflex from the sciatic nerve was desired. A just sufficient amount of the drug, well diluted with normal saline solution, was injected slowly through the external jugular vein. When artificial respiration was employed, the quantity of air used was the least that would keep the blood properly oxygenated. Pos-

[2] Kinjoun and Rosenau: Report of the Public Health and Marine Hospital Service, 1897, p. 762.

[3] Lamar and Meltzer: Journal of Experimental Medicine, 1912, xv, pp. 133–148.

sible errors from ether, curare, and artificial respiration are excluded by the decisive results obtained when none of the three was employed. Much care was used in the preparation and subsequent handling of the nerves. The stimulating current was from an inductorium supplied with constant Daniell cells, and the current strength was that distinctly perceptible to the operator's tongue.

It cannot be too strongly insisted that trustworthy quantitative measurement of vasomotor reflexes requires a degree of care and skill hardly to be attained except after long experience.

OBSERVATIONS UPON THE RABBIT

The greater number of the rabbits were infected with pneumococcus Fränkel, the remainder with streptococcus mucosus.

The pneumococcus infection: The pneumococcus Fränkel, injected into the veins of rabbits, produces a septicaemia. It was this septicaemia in rabbits upon which Romberg and his associates[4] made their experiments. Every fatal pneumonia in man has a pneumococcus septicaemia, usually regarded as the direct cause of death. Observations made on rabbits with pneumococcus septicaemia may therefore reasonably be applied to cases of pneumonia in other animals in which local changes, such as consolidation, appear in the lungs. In rabbits with pneumococcus septicaemia the measurement of the reflexes, to be absolutely convincing, should of course be made during the last hours of life. It is not easy to determine when the rabbit is about to die, nor does the autopsy show how near death was when the experiment was done. It is desirable to choose the hour preceding that in which the rabbit would have died had he not been killed at the end of the experiment.

In our experiments with pneumococcus septicaemia, 7 rabbits were injected with cultures grown on blood serum, and 4 with cultures grown in bouillon. Of the blood serum group, three died in approximately 72, 96, and 96 hours, respectively, and

[4] Romberg, Pässler, Bruhns, Müller: Deutsches Archiv für klinische Medicin, 1899, lxiv, p. 652.

four were used for operation at approximately 48, 72, 96, and 96 hours.

Of the bouillon group, one rabbit died in 48 hours, and the three others were operated upon in approximately 48, 48, and 96 hours. These figures indicate with probability that at least some of the rabbits were at the point of death when their reflexes were measured.

TABLE I

The absolute and percentile change in blood pressure on stimulation of the depressor fibres and the sciatic nerve in rabbits, cats, and dogs.

ANIMAL	INITIAL LEVEL OF BLOOD PRESSURE	DEPRESSOR			SCIATIC		
		Number of observations	Average absolute fall	Average percentile fall	Average percentile rise	Average absolute rise	Number of observations
	mm. Hg		*mm. Hg*	*per cent*	*per cent*	*mm. Hg*	
I. Seven rabbits with pneumococcus-septicaemia	101 to 110	2	33	31	22	23	1
	91 to 100	5	30	32	32	30	4
	81 to 90	7	29	34	36	31	4
	71 to 80	22	31	41	48	36	10
	61 to 70	11	28	43	60	39	10
	51 to 60	7	22	40	87	48	6
	41 to 50	2	21	47	96	43	2
	31 to 40				108	38	2
II. One rabbit with consolidated lung	91 to 100				65	38	1
	81 to 90	3	31	25	33	27	1
	71 to 80	3	21	28			
	51 to 60				30	16	1
III. Four cats with consolidated lung.	141 to 150	2	50	34			
	111 to 120	2	45	39			
	101 to 110	2	28	27			
	91 to 100	2	36	38			
	81 to 90	3	49	58			
	71 to 80	3	41	55	74	55	4
	61 to 70	2	25	38	38	25	4
	51 to 60	2	23	42	55	30	3
IV. One dog with consolidated lung.	141 to 150				24	35	1
	131 to 140				26	35	3
	121 to 130				25	31	7
	111 to 120				25	29	2
	101 to 110				29	30	5

In cats the depressor fibres in the central end of one cut vagus were stimulated. The other vagus nerve was of course also severed.

The clinical picture in the 7 rabbits was significant in 2, but not significant in the remaining 5, except that the rectal temperature in these five was 40°, 40°, 40°, 41.5° and 41°C, respectively. In the rabbits of November 7 and November 9, the clinical evidence was more satisfactory. In the rabbit of November 7, the temperature 80 hours after the injection was 41°; at the 94th hour it was 40°; and at the 96th hour, when the experiment began, it was 38.5°, while the appearance of the animal suggested the approach of death. The rabbit of November 29 had a temperature of 41° and was weak and obviously very sick when placed on the operating table, 72 hours after injection. This rabbit was so ill as to make ether superfluous; the perception of pain was no longer present. Here again, it is reasonable to conclude that some of the rabbits were near death when the reflexes were measured.

Reference to the first series of measurements in Table I shows that in these last hours of the disease, the vasomotor apparatus gave normal depressor and sciatic reflexes.

Rabbits with consolidated lung tissue: In rabbits infected through the veins with the pneumococcus Fränkel there are no well defined stages in the clinical course of the disease, whereas the pseudopneumococcus introduced into a bronchus gives rise to areas of consolidation identical with those seen in pneumonia in human beings. The advantage of the consolidated form is that the vasomotor observations may then be correlated with definite pathological changes easy of recognition.

Of four rabbits infected with the pseudopneumococcus, one died within 5 hours, a second died on the operating board 25 hours after inoculation, the third was operated upon 26 hours after inoculation, and the fourth recovered atfer severe illness. Autopsy of the three rabbits that died showed lobar consolidation in the one that lived 5 hours and consolidated areas distributed throughout the lungs in the two others.

The protocols follow:

Experiment April 13, 1914, 10 a.m. In each of four rabbits, weighing about 2 kilos each, 10 cc. of a 24-hour culture of the pseudopneumococcus in plain, fractionally sterilized broth was injected into a bronchus by means of a soft catheter passed through an incision in the

trachea. The wound was then loosely sewed together and the rabbits returned to the cage in apparently good condition. 3 p.m. One rabbit was found dead. Autopsy showed that the whole right lung was pale red, fairly firm, and that it sank in water. The section surface was dark red, firm, and airless. The other rabbits seemed ill.

April 14, 9.30 a.m. A second rabbit was cyanotic and had labored, grunting respiration. The rectal temperature was 35°. 10.30 a.m. The temperature was 34°. Just after being placed on the operating board the rabbit had convulsive movements which quickly ended in death Autopsy showed that, except for a few minute portions, the whole right lung and one-third of the left lung consisted of mottled, blackish or gray-red, airless, leathery areas. 11.30 a.m. A third rabbit was weak and could only regain the sitting posture with difficulty after being placed on its side. The respirations were grunting and labored, temperature 40°. This animal's vasomotor reflexes were studied during the course of the next two hours. At 12 m., stimulation of the left depressor nerve after previous section of both vagi caused the blood pressure to fall from 78 to 60 mm. Hg. At 12.30 p.m., stimulation of the central end of the sciatic nerve caused the pressure to rise from 83 to 110 mm. Hg and stimulation of the depressor nerve at 1.05 p.m. caused the pressure to fall from 72 to 42 mm. *Autopsy:* Scattered through both lungs, and occupying about half the total lung substance were bright red, fairly firm, airless areas, varying in size from mere points to irregular masses about 15 mm. in diameter, extending deep into the lungs. Similar areas were found throughout the lung substance. The edges of the lung in many places were dark red, firm and dry. *April 16.* The fourth rabbit on April 14, seemed very sick, with temperature of 40°. April 15 it was much better, and on April 16 it appeared to have entirely recovered.

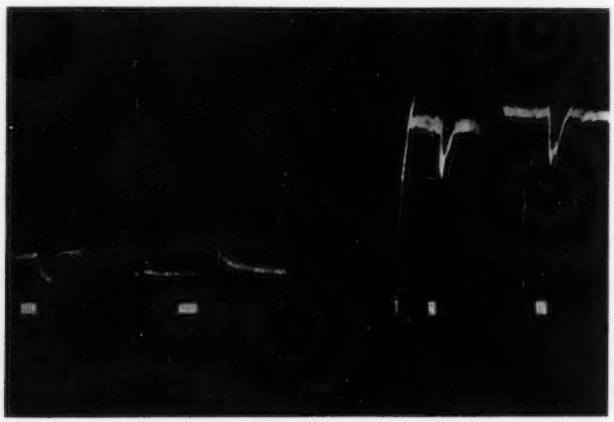
The condition of the vasomotor arc in rabbits with consolidated lung tissue is shown in Table I, from which it appears that the reflexes are not significantly changed from those frequently obtained in normal animals.

In figure 1B, are given two depressor curves from this experiment; the reflex fall is 27 and 30 per cent.

OBSERVATIONS ON CATS

Ten cats were given by the intra-tracheal method 24-hour, cultures of the pseudopneumococcus. Of these, five ultimately recovered, and of the remainder two died in 55 and 48 hours,

and three were operated upon in 31, 24, and 60 hours, respectively. On autopsy, it appeared that all these animals had an acute inflammatory process of the lung tissue, of the bronchopneumonic type. The areas of consolidation were sometimes so closely packed that macroscopically one or more entire lobe appeared to be uniformly solidified. In other cases the areas of consolidation were small and separated by tissue containing air. The exudate was slimy and viscid. The bronchi were generally filled with brownish, ropy mucus, mixed with pus. The clinical picture will be clear from the following protocol.



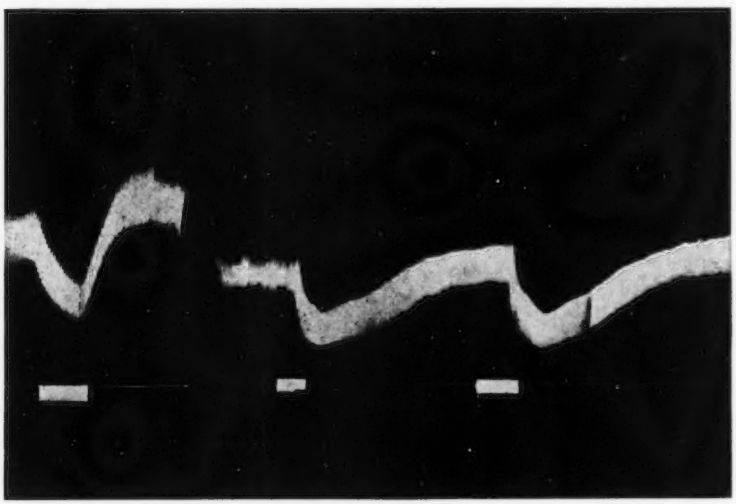
A B

FIG. 1 A, Experiment November 29. Carotid pressure in a rabbit with pneumococcus septicaemia. Membrane manometer. On stimulation of the left depressor nerve (without curare), the carotid pressure, recorded with a membrane manometer fell from 95 to 45 mm. Hg, 53 per cent. On sciatic stimulation (with curare) the pressure rose from 60 to 107 mm., 78 per cent.

B, April 14. From a rabbit with lobar pneumonia (no curare). Depressor stimulation (vagi intact) causes a fall from 82 to 60 mm., 27 per cent, and from 90 to 63 mm., 30 per cent (vagi cut).

Experiment March 17, 1914, 10 a.m. A cat, weighing 3000 grams, was etherized and 25 cc. of a 24-hour culture of the pseudopneumococcus was injected into a bronchus. *March 18, 9.30 a.m.* The temperature was 34°. The respiration was markedly labored and of the type

seen in laryngeal stenosis. The animal was relaxed and lying prone and seemed at the point of death. It was immediately placed on the operating board and given a few whiffs of ether. At 10 a.m., both vagi were cut. At 10.45 a.m. one cubic centimetre of curare was cautiously given. Stimulation of the central end of the left vagus at 11.10 a.m. caused the pressure to fall from 80 to 46 mm. Hg, 43 per cent (fig. 2 A.). At 11.55 a.m., stimulation of the sciatic raised the pressure from 45 to 65 mm., 45 per cent. The animal was now



A B

FIG. 2 A, Experiment March 18. From a cat with lobar pneumonia. Both vagi cut. Curare. The stimulation of the central end of one vagus caused the carotid pressure to fall from 80 to 46 mm. Hg, 43 per cent. Curare.

B, January 2. Cat with lobar pneumonia. Stimulation of depressor fibres in cut vagi causes a fall from 80 to 30 mm. Hg, 63 per cent, and from 82 to 30 mm., 63 per cent. No curare.

killed. *Autopsy:* The total lung area except the tip of the left upper lobe and the extreme edge of two other lobes was mottled gray-red, firm, non-crepitant, and voluminous. The cut surface, also gray-red, was moist and exuded sero-pus. Scattered through the lung were many areas of hemorrhage and necrosis. The liver contained very

many small foci of hemorrhage. The spleen was large and soft. The pericardium and endocardium showed several small areas of hemorrhage.

The reflexes obtained from cats are averaged in Table I. part 3. As in the other animals they are obviously normal, Excellent examples are seen in figure 2 B and in figure 3.

OBSERVATIONS ON DOGS

Satisfactory infections were obtained in five dogs. In three of these, at the end of 25, 28, and 24 hours, the rectal temperature

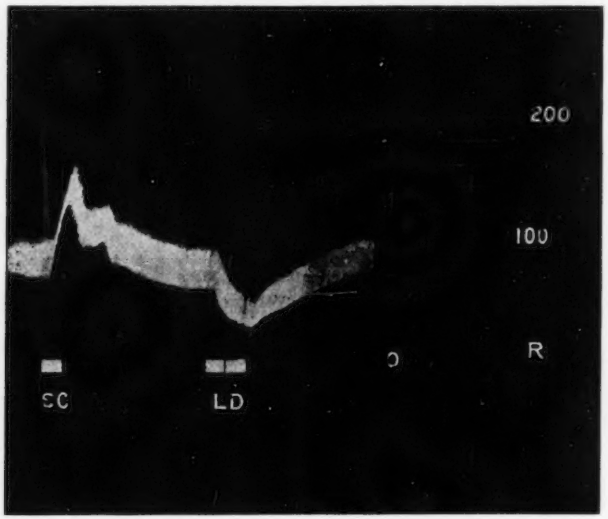


FIG. 3 January 2. Cat with lobar pneumonia. Sciatic stimulation causes a rise from 68 to 130 mm. Hg, 91 per cent. Stimulation of depressor fibres in cut vagi causes a fall from 60 to 32 mm. Hg, 47 per cent. To the right, a scale obtained by graduating the membrane manometer against a mercury column. R is the return of the writing point to atmospheric pressure.

was 34°, 36° and 34°, the breathing shallow and very difficult and the upright position impossible. In this collapsed state, the animals were killed merely by being placed on the operating board. In a fourth dog, the disease ran a slower and more practicable course. This animal was operated upon 55 hours after infection,

but on being given curare, developed Traube-Hering waves of much intensity. On stimulation of the sciatic nerve a clearly normal reflex was obtained. On autopsy, the right lower lobe, one-third of the right middle lobe and half the left lower lobe were consolidated. Following is Dr. James Homer Wright's description of two microscopic sections from one of the consolidated areas (fig. 4 A and B).

Two sections. The majority of the air cells are filled with an exudate consisting chiefly of polymorphonuclear leucocytes together

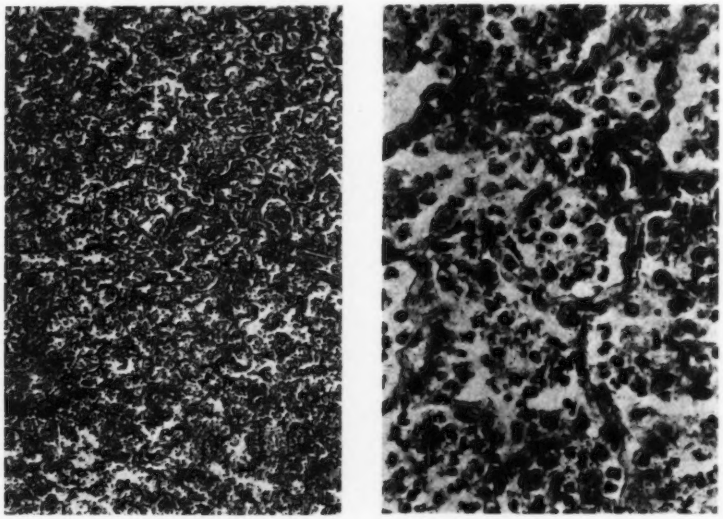


FIG. 4 March 4, 1914. Sections from the lung of a dog with lobar pneumonia. The microscopic appearances are described in the text. On stimulation of the sciatic nerve, a normal reflex rise of blood pressure was observed.

with some endothelial leucocytes and desquamated alveolar epithelium. The air cells contained in this exudate occupy larger and smaller areas in the sections and appear to be in relation with certain of the smaller bronchi. A minority of the air cells contain granular coagulum, or smaller numbers of the above mentioned cells, or are practically empty. Very little fibrin is present. Some of the air cells show more or less

collapsed areas. There is marked engorgement of the capillaries generally.

The bronchi generally are filled with closely packed cells, the great majority of which are polymorphonuclear leucocytes. There is little or no desquamation of the bronchial epithelium.

The histological appearances in these two sections are those of a confluent broncho-pneumonia producing grossly the appearance of a homogeneous consolidation.

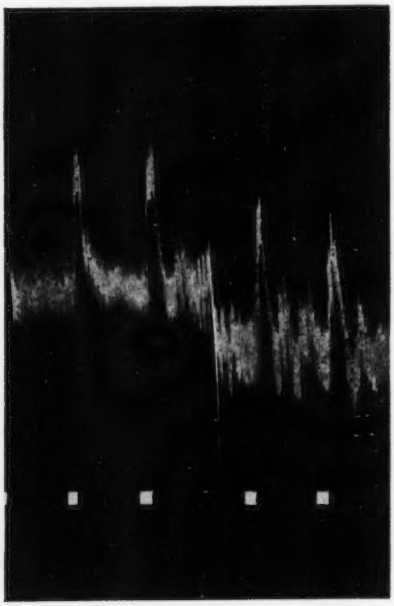


FIG. 5 February 26. From a dog with lobar pneumonia. Carotid pressure recorded with a mercury manometer. The horizontal line is at 75 mm. pressure. On stimulation of the sciatic nerve the pressure rose 37, 38, 38, and 40 mm. Hg, 29, 26, 36, and 39 per cent. The lungs of this dog are shown in figure 6.

A fifth dog, operated upon February 26, furnished the measurements given in Table I, section 4, and in figure 5. The protocol of this experiment is as follows:

Experiment February 24, 1914, 3.30 p.m. A dog, which weighed 5500 grams and whose rectal temperature was 38.5°, was given 0.015 gram morphine sulphate subcutaneously. At 3.50 p.m., the dog was etherized and 22 cc. of a 24-hour culture of the pseudopneumococcus injected into a bronchus. *February 25, 3.30 p.m.* The temperature was 40°. The animal was listless and refused meat. *February 26,*

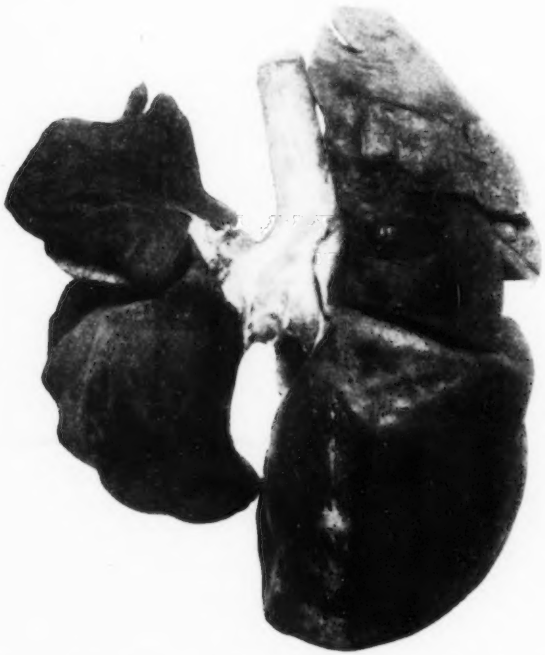


FIG. 6 Lungs of the dog operated upon February 26. The lowest lobe on the right side is wholly consolidated and there are large consolidated areas in the other lobes, except the uppermost. Normal reflex increases on stimulation of the sciatic in this dog are shown in figure 5.

11 a.m. The temperature was 39° and the dog was coughing and breathing rapidly. 4 p.m. The temperature was 40°. The breathing had become labored and irregular. At 4.15 p.m. the dog was placed on the operating board; no ether was used because the animal was insensible to pain. Four stimulations of the left sciatic nerve

caused the pressure to rise respectively from 127, 129, 107 and 103 to 164, 163, 145 and 143 mm. Hg. *Autopsy:* The whole lower lobe of the right lung and several areas in all the other lobes, with the exception of the two upper, were firm, voluminous, gray-red, non-crepitant, and sank in water (fig. 6). The section surface was dry, gray-red, and non-crepitant.

It is evident that in the dog, as in the rabbit and cat normal reflexes[5] are found in animals near death with pneumonia.

CONCLUSION

Experimental evidence proves that the vasomotor centre is not impaired in fatal pneumonia.

[5] The reflex rise in blood pressure following sciatic stimulation in the dog is normally less than in the rabbit and cat. (W. T. Porter: this JOURNAL, 1908, xxiii, p. 136.)

COMPENSATORY PHENOMENA IN THE DISTRIBUTION OF THE BLOOD DURING STIMULATION OF THE SPLANCHNIC NERVE

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A study of the transfer of the blood from the arterial to the venous side, during periods of vasoconstriction affecting the splanchnic area, requires the special consideration of two factors; namely, the quantity of blood that flows through the portal circuit, and the quantity of blood that traverses other divisions of the circulatory system.

The blood flow in the portal vein of the dog has been carefully studied by Burton-Opitz,[1] measurements having been made upon the flow in the main trunk as well as in the tributaries. It has been shown that vasoconstriction in the abdominal viscera causes a marked diminution in the portal flow. The amount of decrease during a period of about 20 seconds of moderate stimulation of one splanchnic nerve was as much as one-fourth of the quantity normally flowing through this vein. In work upon the magnitude of the portal flow it is stated "that a dog having an average body weight of 14.3 kgm. possesses a portal flow of 268.2 cc. per minute." If we assume that the total quantity of blood is one-thirteenth of the body weight, it is obvious that about one-fourth of the entire blood-supply normally passes through the portal circuit. This would mean that about one-sixteenth of the blood of the animal, or approximately

[1] Burton-Opitz: Archiv für die gesammte Physiologie, cxxiii, p. 553, 1908; cxxiv, p. 495, 1908; cxxix, p. 189, 1909; cxxxv, p. 205, 1910; and Quarterly Journ. Physiol., 1911, iv, p. 113.

68 cc. per minute, must find its way into the venous channels during splanchnic vasoconstriction through some other course, because the accumulation of this quantity of blood on the arterial side would soon produce a greatly diminished venous return to the heart and consequently a diminished ventricular output.

The large vascular area over which the splanchnic nerve exercises a powerful vasomotor influence, has been regarded as occupying a reciprocal relation to other parts of the body. Thus Dastre and Morat[2] state that a vasoconstriction in the abdominal portal vessels is accompanied by a dilatation of the cutaneous vessels, and they postulate that a vasoconstriction of the cutaneous vessels denotes a dilatation of the splanchnic area. A similar view has been expressed by Bayliss and Bradford[3] who state that there is an antagonism of a physiological character existing between the vessels of the limb and those of the splanchnic area—the latter exercising the predominant influence. v. Anrep[4] similarly describes the splanchnic nerve as the regulator of the blood-supply of the body.

By means of the plethysmographic method it has been demonstrated that the volume of the intestine,[5] kidney,[6] and spleen,[7] is greatly diminished during stimulation of the splanchnic nerve, and a similar phenomenon has been shown with the hind limbs.[8] These observations are of interest in this connection because of the bearing they have upon the use of the changes in the volume of an organ as an index of the quantity of blood flowing through it. If an increase or a decrease in volume were an infallible index of respective changes in the blood-flow, then obviously the simultaneous diminution in the volume of the internal organs and the extremities would produce a condition of arterial stagnation. The present paper presents some results of a study of the blood-flow through other parts of the body during periods

[2] Dastre and Morat: Arch. de Physiol., 1882, p. 337.
[3] Bayliss and Bradford: Journ. Physiol, 1894, xvi, p. 10.
[4] v. Anrep: Journ. Physiol., 1912, xlv, p. 307.
[5] Hallion and Francois-Franck: Arch. de Physiol., viii, p. 493.
[6] Cohnheim and Roy: Arch. f. Pathol. Anat., xcii, p. 424, 1882.
[7] Roy: Journ. Physiol., 1880-82, iii, p. 203.
[8] Bayliss: Journ. Physiol., 1902, xxviii, p. 220 and v. Anrep; loc. cit. p. 310.

in which there is a lessened flow through the portal circuit. I have experimented with the circuits of the head and posterior extremity. Measurements of the blood-flow were taken from the carotid artery, jugular vein, femoral artery, and femoral vein. The data obtained from these divisions of the circulatory system enable us to determine the extent of compensation for the diminished transfer of blood through the portal circuit.

Method of investigation. The experiments were performed upon dogs weighing 6 to 12 kgm. Narcosis by means of ether was maintained in all animals throughout the experiments. The general blood-pressure was determined in the left femoral artery by means of a mercury manometer. The left greater splanchnic nerve was exposed through the peritoneal cavity, isolated for about 1 cm. centrally to the left suprarenal capsule, and placed in shielded electrodes. In some experiments the nerve was divided and in others it was left intact, but in the two cases the general character of the results did not differ materially.

At the outset information was sought regarding circulatory conditions by registering venous pressures in different parts of the body. Such determinations, however, serve only as an index of qualitative changes in the volume of the blood-flow through a part; for example, an increased venous pressure is indicative of a greater flow, and decreased pressure an indication of a lessened flow. In addition I have made quantitative determinations of the blood-flow in the circuits of the head and posterior extremity by means of the recording stromuhr described by Burton-Opitz.[9]

The determinations of venous pressure were made in all cases by means of an ordinary manometer filled with saline solution and connected in most cases with the blood-vessel by means of a T-canula. The readings were made at short intervals and inserted directly beneath the tracing of the arterial blood pressure.

[9] Burton-Opitz: Arch. f. d. gesammte Physiol., 1908, cxxi, p. 150.

OBSERVATIONS OF VENOUS PRESSURE

1. Femoral vein. Vasoconstriction in the splanchnic area produces a gradual increase in the lateral blood pressure in this vein which attains its maximum value shortly after the maximum height of the systemic arterial pressure has been reached. It is followed by a fall, which is essentially identical in character with the phase of increasing pressure. While the changes in venous pressure pursue a course that is practically parallel to that of the arterial pressure, a slight difference in the time relationship is noticeable. For example, an average of a series of ten readings taken after stimuli of slightly different intensity and duration, shows the maximum arterial pressure in twenty-four seconds after the beginning of the stimulation, while the corresponding venous readings show the maximum pressure in thirty-three seconds after the beginning of the stimulation.

The readings of arterial pressure in this set of experiments show an average increase of 25.2 mm. Hg, while the average venous pressure is 13 mm. water or approximately 0.96 mm. Hg. This increase in venous pressure is proportionally large, because the average normal pressure in this series of experiments was 4.9 mm. Hg, a value that may be regarded as representing a normal pressure since it is only 0.5 mm. Hg less than the average pressure obtained by Burton-Opitz[10] in eighteen dogs ranging in weight from 6 to 24 kgm.

In table I are compiled the changes in pressure in the femoral vein upon stimulation of the splanchnic nerve.

In view of the work of v. Anrep[11] upon the relation between the changes in the volume of the posterior extremity and the activity of the adrenal glands, I have paid especial attention to any possible change in venous pressure coincident with the second phase in the rise of arterial blood-pressure. I have been unable to observe any indication of an alteration in the blood-flow at this period. v. Anrep attributes the secondary rise in general pressure which follows stimulation of the splanchnic, to

[10] Burton-Opitz: Amer. Journ. Physiol., 1903, ix, p. 198.
[11] v. Anrep: loc. cit. p. 310.

TABLE I

EXPERIMENT	NERVE STIMULATED	DURATION OF STIMULATION IN SECONDS	SECONDS AFTER BEGINNING OF STIMULATION	PRESSURE IN FEMORAL ARTERY IN MM. Hg.	PRESSURE IN FEMORAL VEIN IN MM. H_2O
I	L. splanchnic nerve undivided	27		74	85
			6	84	90
			17	90	95
			27	84	100
			32	76	95
			41	70	90
			47	70	85
II	L. splanchnic nerve undivided	40		90	80
			9	74	85
			23	80	95
			34	72	93
			39	70	90
			51	68	85
III	L. splanchnic nerve divided	53		95	65
			6	114	70
			11	120	80
			25	146	85
			37	144	80
			50	132	72
			102	102	70
			108	98	65
IV	L. splanchnic nerve undivided	46		130	50
			16	166	55
			24	168	55
			32	160	60
			40	154	55
			58	134	55
			66	134	50
V	L. splanchnic nerve divided	37		66	50
			11	76	55
			26	88	60
			36	80	64
			45	72	60
			64	66	55
			82	66	50

a powerful vasoconstriction in the peripheral blood vessels as a result of an increased quantity of adrenalin in the circulating blood at this time. In support of this view he has shown a decrease in the volume of the extremities. If the diminished volume of the posterior extremities were accompanied by a marked decrease in the transfer of blood within the limb, we would expect to obtain a drop in the blood-pressure in the femoral vein following closely upon the second phase in the arterial blood-pressure rise. But the absence of such a drop in pressure should not be interpreted, I believe, as opposed to the conclusions of v. Anrep; on the contrary, it indicates that changes in the volume of the posterior extremity cannot be relied upon to give an index of the quantity of blood flowing through it.

2. External jugular vein. It has been shown by Tschuewsky[12] that the blood supply of the head is about four times greater than that of the posterior extremity. If one reasons from analogy, it is evident that the head must play an important part in compensating for the diminished transfer of blood through the portal system. The external jugular vein was selected, because it is the principal vessel for the return of blood from the head.

The results obtained from five experiments on the external jugular vein are arranged in table II.

It will be seen that there is a marked increase in pressure during the stimulation of the splanchnic nerve, which is evident in this particular set of experiments as an average rise in pressure of 1.8 mm. Hg. If contrasted with the increase in femoral venous pressure, the external jugular vein shows an absolute rise that is much greater. The quantitative variation in pressure indicated in this table is characteristic of all of the experiments upon this vein. It can readily be observed that the difference in the degree of increase in the three different animals from which these observations were taken is comparatively small.

The rate of increase in pressure in the external jugular vein as compared with that in the femoral is significant in showing

[12] Tschuewsky: Arch. f. d. gesammte Physiol., 1903, xcvii, p. 386.

TABLE II

EXPERIMENT	NERVE STIMULATED	DURATION OF STIMULATION IN SECONDS	SECONDS AFTER BEGINNING OF STIMULATION	PRESSURE IN FEMORAL ARTERY IN MM. Hg	PRESSURE IN FEMORAL VEIN IN MM. H_2O
				60	20–
			7	76	15–
			12	80	10–
			14	80	5–
			18	88	0
I	L. splanchnic nerve undivided	28	23	90	5
			30	82	0
			33	76	5–
			38	64	10–
			44	60	15–
				66	20–
			5	82	15–
			9	92	10–
			12	96	5–
			14	98	0
II	L. splanchnic nerve undivided	30	20	102	5
			33	86	0
			36	78	5–
			39	72	10–
			44	68	20–
				56	5–
			4	70	0
			7	72	5
			12	72	10
III	L. splanchnic nerve undivided	17	26	70	13
			30	64	10
			42	58	5
			68	60	0
				86	20–
			5	104	15–
			10	120	10–
			14	120	5–
			16	120	0
			19	118	5
IV	L. splanchnic nerve divided	37	24	116	10
			30	110	12
			46	100	10
			53	96	5
			62	94	0
			77	98	5–
				136	30
			2	140	35
			6	156	45
			9	162	50
V	L. splanchnic nerve undivided	37	12	162	55
			26	152	50
			35	140	45
			41	136	40
			64	136	30

a very close relationship between the two. For example, the time required for a 5-mm. increase in pressure in each vein is directly proportional to the total increase in pressure in each vein. It is evident, therefore, that the accelerated flow through the limb and that through the head are dependent upon essentially identical haemodynamic factors. Moreover, the comparatively large jugular flow might well be expected to show any temporary fluctuations in pressure that would result from a vasomotor action either in other parts of the body exclusive of the splanchnic area, which would tend to shift the blood-stream, or any possible vasomotor changes that might occur in the head circuit. The uniform character of the records during the entire phase of changed pressure makes the existence of such secondary alterations extremely doubtful.

The absence of secondary variations in the blood-pressure, and particularly of a decrease, is taken to mean that the circuit of the head offers at no time an effectual hindrance to the blood-flow through this part. Furthermore the degree of increase in pressure in the external jugular vein, permits of rating the head circuit as a most important factor in counterbalancing the diminished transfer of blood through the portal system.

In some experiments venous pressures were determined in the vicinity of the right auricle by inserting a catheter through the right external jugular vein into the superior vena cava. The most striking feature of these measurements is an initial rise in pressure amounting to only from 5 to 10 mm. of water. Subsequently the pressure returns rapidly to normal, and may even at times reach a value very slightly below the normal for a short period. It is evident, therefore, that the change in blood-pressure close to the heart is very slight. The temporary increase is probably due to a squeezing out of the blood from the portal vessels from vasoconstriction in the splanchnic area. From these considerations it appears that other channels have equalized the transfer of blood so that the pressure close to the heart, and therefore, the volume of the blood returned, is affected very little.

3. Pancreatic and renal veins. A few experiments were made upon these veins to obtain information regarding the pressure

conditions in them, because they represent venous channels in which a decrease in the blood-flow is known to occur during splanchnic vasoconstriction. The results were somewhat varied, showing in some cases fairly regular, in others fluctuating changes.

One set of readings (table III) will illustrate the essential character in the pancreatic vein.

It will be noted that the changes in venous pressure occur simultaneously with those in the general pressure, but in an inverse relation. While the fall in pressure was not always so great as shown in this set of readings, an initial drop was observed in every case—a result the opposite of that obtained with the femoral and jugular veins.

Similarly in the renal vein there was obtained a drop in pressure. In this case, however, the fall was usually small and after

TABLE III

Left divided splanchnic nerve stimulated for twenty-three seconds

Seconds after beginning of stimulation		11	16	21	32	36	40
Pressure in femoral artery in mm. Hg	86	110	118	124	116	112	108
Pressure in pancreatic vein in mm. H_2O	100	95	90	80	90	100	110

this initial drop of a few millimeters there was in many cases a partial return to the normal before the rise in general pressure reached a maximum. It is evident from readings taken from the central end of the renal vein, and from a catheter inserted into the inferior vena cava, that the pressure does not change markedly in the latter vessel during vasoconstriction in the splanchnic area. The pressures in the renal vein were of necessity measured close to the vena cava, therefore the small drop in renal pressure was due, I believe, to the equalizing tendency of the nearly uniform pressure in the large vena cava.

The experiments upon the pancreatic and renal veins show an unmistakable drop in pressure. The fall is in many cases small but the principal significance lies in the fact that it shows a direct relationship between the changes in venous blood-pressure and the volume of the blood-flow.

MEASUREMENTS OF THE BLOOD-FLOW

1. Flow through the head. The experiments upon the blood-pressure in the external jugular vein gave results that indicate an increased flow through the head during stimulation of the splanchnic nerve. The method, however, was not applicable to quantitative determinations. The experiments now to be described were undertaken with this end in view. It was also hoped that the data obtained would give information regarding the proportional amount of compensation for the diminished portal flow which is afforded by the head circuit.

The blood-flow in the external jugular vein was taken as the index of flow through the head, because it is the principal vessel for the return of the blood from this part. In the results of these experiments three things are obvious—first, vasoconstriction in the splanchnic area produces a marked increase in the blood-flow through the head; second, the changes in the flow occur in the same general manner as the changes in blood-pressure within the vein; and third, there is no evident diminution in the flow coincident with the second phase in the increase in arterial blood pressure.

It will be seen from table IV that the average blood-flow prior to the stimulation of the splanchnic nerve was about 1.99 cc. in a second and the average systemic blood pressure corresponding to this blood-flow was 0.89 mm. Hg. In terms of a systemic pressure of 100 mm. Hg, this would give a flow of 2.23 cc. per second, a value that is close to the average normal of 2.4 cc. per second obtained by Burton-Opitz.[13] Stimulation of the splanchnic nerve with current of moderate strength for an average period of forty-four seconds gave an increase of about 12.5 per cent in the amount of blood-flow through this vein.

In table IV are arranged the results of five experiments upon the flow in the jugular vein.

Let us turn for a moment to the proportional compensatory action afforded by this circuit. If we take the average normal flow in the external jugular as 144 cc. per minute, 2.4 cc. per

[13] Burton-Opitz: Amer. Journ. Physiol. 1902, vii, p. 435.

TABLE IV

Experiment 1

PHASE OF STROMUHR	DURATION OF PHASE	QUANTITY OF BLOOD PER PHASE	QUANTITY OF BLOOD PER SECOND	PRESSURE IN FEMORAL ARTERY IN MM. Hg.	CONDITIONS
	seconds	*cc.*	*cc.*		
1	10.2	21.75	2.13	82	Before stimulation of left splanchnic nerve
2	13.6	21.75	1.60	82	
3	12.0	21.5	1.79	82	
4	12.4	21.75	1.75	95	During stimulation
5	9.8	21.75	2.22	104	
6	10.4	21.50	2.06	106	
7	9.5	21.75	2.28	106	
8	11.0	21.75	1.97	106	
9	10.5	22.5	2.14	100	After stimulation
10	12.2	22.5	1.84	94	
11	12.8	21.75	1.62	90	
12	14.0	21.2	1.51	88	

Experiment 2

1	9.2	21.0	2.28	70	Before stimulation of left splanchnic nerve
2	10.4	19.7	1.89	70	
3	9.8	20.0	2.05	72	
4	10.0	20.5	2.05	80	During stimulation
5	8.2	21.5	2.62	84	
6	9.0	20.7	2.30	90	
7	7.6	21.5	2.83	94	
8	8.8	21.7	2.41	96	
9	6.2	20.2	3.25	98	
10	8.5	19.5	2.29	94	After stimulation
11	7.5	20.7	2.76	90	
12	10.8	22.0	2.10	86	

Experiment 3

1	12.4	20.75	1.67	84	Before stimulation of left splanchnic nerve
2	20.0	21.2	1.06	84	
3	13.6	21.2	1.56	98	During stimulation
4	17.0	21.75	1.28	106	
5	11.2	21.5	1.92	106	
6	16.5	21.0	1.27	104	After stimulation
7	15.0	20.75	1.38	98	

TABLE IV—Continued

Experiment 4

PHASE OF STROMUHR	DURATION OF PHASE	QUANTITY OF BLOOD PER PHASE	QUANTITY OF BLOOD PER SECOND	PRESSURE IN FEMORAL ARTERY IN MM. Hg.	CONDITIONS
	seconds	*cc.*	*cc.*		
1	11.8	22.2	1.96	76	Before stimulation of left splanchnic nerve
2	15.6	21.2	1.36	76	
3	11.5	21.0	1.73	76	During stimulation
4	14.0	21.75	1.55	94	
5	9.5	22.5	2.36	98	
6	13.8	22.0	1.59	100	
7	9.3	21.2	2.27	100	After stimulation
8	16.0	21.5	1.33	88	

Experiment 5

1	8.4	20.0	2.38	136	Before stimulation of left splanchnic nerve
2	5.2	19.7	3.78	136	
3	6.8	19.7	2.89	136	
4	5.5	19.2	3.48	136	
5	7.5	18.7	2.49	136	
6	5.0	18.7	3.74	144	During stimulation
7	6.8	19.2	2.82	154	
8	5.2	19.7	3.78	160	
9	8.4	19.5	2.32	144	
10	5.5	19.5	3.54	122	
11	8.5	19.2	2.25	120	After stimulation
12	7.5	18.7	2.65	130	

second, then during the period of stimulation of the splanchnic nerve there is an increase of approximately 17 cc. in a minute. The compensation offered by the head circuit as figured on this basis would amount to 34 cc. in a minute for the two external jugular veins. This value, however, would probably not represent the total compensation afforded by the head portion of the circulatory system, because the internal jugulars may be expected to take a part proportional to their normal volume of flow. Bearing in mind now the fact stated in the early part of this paper that splanchnic vasoconstriction may produce a diminished transfer of blood through the portal circuit, to the extent

of about 68 cc. in a minute, it is obvious that the head circuit alone is capable of compensating for more than one-half of this quantity.

The average flow in these experiments during stimulation of the splanchnic nerve was 2.26 cc. per second, and the average systemic pressure for the same period, obtained by taking the mean pressure for each phase of the stromuhr, was 107 mm. Hg. These values give a volume of flow per 100 mm. Hg pressure, of 2.11 cc. per second. If we now compare this with the normal flow of 2.23 cc. per second, obtained in these experiments, it is evident that there is a greater volume of flow per second with

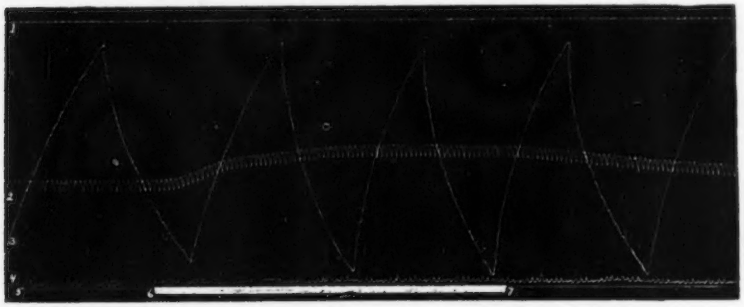

FIG. 1 RECORD OF THE ACCELERATED BLOOD-FLOW IN THE EXTERNAL JUGULAR VEIN DURING STIMULATION OF THE L. SPLANCHNIC NERVE

1, Time in seconds; *2*, blood-pressure in femoral artery (mercury manometer); *3*, stromuhr; *4*, blood-pressure in jugular vein (membrane manometer) *5*, zero blood pressure; *6* to *7*, period of stimulation.

the high systemic blood-pressure, yet in proportion to the head of pressure there is a diminished efficiency. The increase in the flow bears a close relation to the corresponding changes in blood-pressure, as is illustrated in figure 1. There is first a short latent period which is followed by a gradually increasing flow. The maximum flow is usually attained at about the time of highest systemic blood-pressure. If the period of stimulation is short, e.g., ten to fifteen seconds, the maximum flow does not appear until after the cessation of the stimulation.

The graphic tracing of the blood-flow, with respect to the two phases in the increase of systemic blood-pressure, shows no indication of a variation that could be associated with a vasomotor activity in the carotid circuit. The first phase in the rise of blood-pressure is so short that it is questionable whether its effect could be demonstrated with the stromuhr, but in case of the second phase, there is obviously no marked change in the volume of blood-flow. If the diminished volume of the extremities, said to occur at this time, were accompanied by a pronounced decrease in the blood-flow in these parts; then secondary alterations in the already accelerated blood flow through the head circuit might be expected to occur. The fact that no such secondary changes in the flow have been recorded in these experiments, if taken together with the results obtained upon the femoral vein which are to follow, support the view that the volume decrease of the limb is insufficient to cause a marked change in the blood-flow through these parts.

2. Flow through the posterior extremity. This series of experiments was made upon the femoral vein and femoral artery. In brief the results show an increased flow through this part during splanchnic stimulation, and no retardation coincident with the second rise in general blood-pressure. The total compensation through this circuit is much smaller than that afforded by the head circuit, because the total blood-flow is relatively small.

Femoral vein. The average obtained from five experiments upon the flow in this vein shows an increase of a fraction less than 15 per cent with an initial mean systemic pressure of 91 mm. Hg, a period of stimulation of thirty-three seconds, and a mean systemic pressure during this period of 130 mm. Hg. The graphic record of this increase in blood-flow is very similar in character to the record of the same phenomenon in the jugular vein. Likewise there is shown in the actual percentage increase in the blood-flow in the two cases a difference of about 2.5 per cent which is well within the limit of experimental error.

The average normal blood-flow in the femoral has been determined[14] as 0.85 cc. per second This value taken with the per-

[14] Burton-Opitz: Amer. Journ. Physiol., 1903, ix, p. 161.

centage of increase obtained in this set of experiments permit of quantitative data upon the compensatory flow through the posterior extremities. Each extremity upon this basis would afford a compensation of about 7.6 cc. per minute or 15.2 cc. per minute for the two posterior extremities. If we assume that the circulation of the anterior extremity gives an increase of blood flow, during stimulation of the splanchnic nerve, approximately the same as obtained from the posterior extremity, the total quantity of blood prevented from returning to the venous side by way of the portal vein (see p. 15) during vasoconstriction in the splanchnic area, is practically all compensated for by the circulations of the head and extremities.

In table V are compiled data from four experiments to show the increase in flow in the femoral vein during the period of stimulation of the splanchnic nerve.

A final feature evident from the records of the experiments now under discussion is a lack of correlation between the rate of the blood-flow through the limb and the changes, said to occur, in its volume. It has been demonstrated[15] that the second phase in the general rise of blood-pressure resulting from stimulation of the splanchnic nerve is accompanied by a diminished volume of the limb, and such changes have been associated with a diminished blood-flow. But in my experiments the blood-flow was not diminished at this phase in the blood-pressure rise; on the contrary the flow was always accelerated during the entire phase of raised systemic blood-pressure, and in many cases the maximum flow was recorded towards the end of or immediately following the second phase in the blood-pressure increase. This fact has a greater significance when the total blood exchange is considered. A diminished volume of some of the abdominal organs has already been referred to on page 16, and moreover it has been shown[16] that in these organs there is a decrease in blood-flow following stimulation of the splanchnic nerve. If the volume of the limb were likewise accompanied by a significant diminution in the blood-flow through it, then the circulation of

[15] v. Anrep: loc. cit. p. 307.
[16] Burton-Opitz: loc. cit.

TABLE V

Experiment 1

PHASE OF STRO-MUHR	DURATION OF PHASE	QUANTITY OF BLOOD PER PHASE	QUANTITY OF BLOOD PER SECOND	PRESSURE IN FEMORAL ARTERY	CONDITIONS
	seconds	*cc.*	*cc.*	*mm.*	
1	22.0	18.7	0.85	114	Before stimulation of left splanchnic nerve
2	23.0	18.5	0.80	114	
3	17.0	17.2	1.0	124	During stimulation
4	12.5	17.5	1.40	124	
5	11.0	19.5	1.70	110	
6	15.0	19.5	1.30	108	
7	17.0	8.7	1.10	106	After stimulation

Experiment 2

1	25.0	18.0	0.72	114	Before stimulation of left splanchnic nerve
2	21.5	18.0	0.86	122	During stimulation
3	16.6	19.0	1.14	126	
4	14.5	19.2	1.32	118	
5	19.3	19.72	1.00	112	After stimulation
6	24.2	17.2	0.71	112	

Experiment 3

1	38.0	15.5	0.40	90	Before stimulation of left splanchnic nerve
2	12.0	5.5	0.46	94	
3	19.0	11.0	0.60	108	During stimulation
4	22.0	18.0	0.82	104	
5	25.0	18.5	0.74	118	After stimulation

Experiment 4

1	22.8	21.0	0.91	84	Before stimulation of left splanchnic nerve
2	17.2	20.7	1.20	84	
3	18.2	22.2	1.22	86	During stimulation
4	9.3	23.0	2.5	106	
5	11.8	22.2	1.88	104	
6	10.0	21.5	2.15	94	
7	13.2	21.2	1.60	90	After stimulation
8	12.0	22.0	1.66	90	
9	14.2	21.5	1.51	90	
10	13.2	20.5	1.55	90	

the extremities would antagonize the circulation of the splanchnic area and there would result a greatly lessened transfer of blood to the venous side. The pressure conditions in different parts of the venous system, as set forth in the first part of this paper, indicate that the venous return is not materially lessened during splanchnic vasoconstriction.

The absolute decrease in the volume of the limb is not evident in the studies[17] upon this subject. But from the method employed in registering this change, and the solid character of the organ itself, it seems probable that the change is very small. From these considerations the conclusion seems warranted that the diminution in the volume of the limb is not sufficient to affect appreciably its blood-flow.

Femoral artery. A few experiments were made upon the blood-flow in this artery to determine whether the inflow to the posterior extremity corresponds, at all closely, to the outflow; since the possibility exists that a part of the accelerated outflow may be due to a squeezing out of the contained blood from vasoconstriction in this organ. The records show an increase in the arterial blood-flow, which is essentially identical in character with that obtained from the femoral vein. An average of three experiments shows an increase of 16.8 per cent, a value that is likewise very close to similar determinations upon the femoral vein. In fact this uniformity in the general character of the records, and the close agreement in the percentage increase in the blood-flow, are the most significant features of the results. These observations make it probable that the accelerated flow in the femoral vein is independent of mechanical factors within the limb.

3. Flow through a denervated kidney. In this series of experiments the left kidney was used in all cases. It was isolated from nervous influences by dividing all the nerve fibers leading to it. The blood-flow through such an organ might be expected, a priori, to follow the changes in general blood-pressure. I proceeded to investigate this by first making use of the oncometric

[17] Bayliss: loc. cit. p. 222; v. Anrep: loc. cit. p. 310.

method to record the changes in the volume during stimulation of the splanchnic nerve. In this feature my results agree essentially with those of v. Anrep. Figure 2 shows a graphic record of a typical experiment of this kind. Here the rapid increase in volume during the initial rise in systemic pressure is attributed to a passive dilatation of the blood-vessels produced by the increased systemic blood-pressure. The sudden decrease in the volume coincident with the second phase in the rise of general blood-pressure is attributed to the augmented secretion of ad-

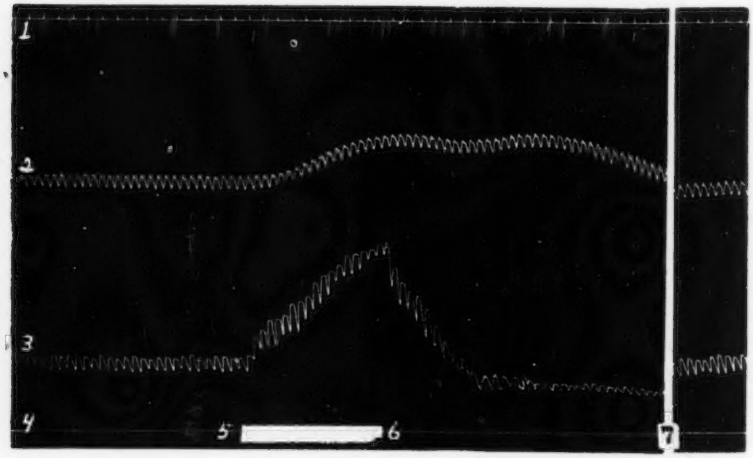

FIG. 2 RECORD OF THE CHANGES IN THE VOLUME OF A DENERVATED KIDNEY DURING STIMULATION OF THE L. SPLANCHNIC NERVE

1, Time in seconds; *2*, blood-pressure in femoral artery (mercury manometer); *3*, volume of the kidney (oncometer); *4*, zero of blood pressure; *5* to *6*, period of stimulation; *7*, interval of 40 seconds.

renalin from stimulation of the splanchnic nerve. This phase, namely, the decrease in the volume, I have been able practically to abolish by using a short series of stimulations. Each stimulation was maintained for a period of about twenty seconds, and repeated four to six times at intervals of about fifty seconds. In this case the supply of adrenalin had evidently become ex-

hausted, because the splanchnic vasomotor mechanism was still capable of producing the initial rise in general pressure but the secondary rise was not shown.

In order to determine whether there is a correlation between these changes in volume of the kidney and the quantity of blood traversing it, I made records of the blood-flow by inserting the stromuhr into the renal vein. The results show a moderate increase in flow during practically one phase of the record of the stromuhr. This increase follows very closely upon the application of the stimulation to the splanchnic nerve, and its duration is apparently identical with the increase in the volume described above. Subsequently there is a marked diminution in the flow, which continues during the remainder of the stimulation period and for a time thereafter. In fact this retarded, yet gradual, return to the normal flow is one of the striking features of the experiment. The decrease in flow occurs simultaneously with the second phase in the rise in systemic blood-pressure. In this feature it coincides, therefore, with the decrease in the volume of this organ described by v. Anrep and corroborated by experiments given in this paper. It can hence be accepted without question that this diminished blood-flow is produced by the action upon the renal blood vessels of the adrenalin, which is present in the circulating blood in larger quantities at this time.

The observations described above make it, I think, clear that the rate of the blood-flow through a denervated kidney does not passively follow the rise in general blood pressure, as it might at first thought be expected to do. In this feature my records differ slightly from those obtained by Burton-Opitz[18] but this discrepancy is more apparent than real since it has been shown that the decrease in flow occurs during longer periods of time than were used in the experiments of Burton-Opitz. Further it is to be noticed that there is an unquestionable relationship between the relative volume of this organ, and the quantity of blood flowing through it at any given time during the period of splanchnic stimulation. This is no contradiction to the conclu-

[18] Burton-Opitz: Arch. f. d. gesammte Physiol., 1909, cxxvii, p. 143.

sion reached on page 32 regarding the change in the volume of the posterior extremity and its blood-flow. The two cases are essentially different, in that the kidney presents a small, flaccid, and highly vascular organ, in which the absolute changes in volume are proportionally large; while the limb is large its tissue is much firmer in character, and from the evidence obtainable it appears that the absolute changes in volume are proportionally small. For these reasons it seems probable, that the total vascular area of the limb would be insufficiently affected by the diminution in volume, from the increased adrenalin in the blood, to produce a retarding action upon the blood-flow through it.

The facts here reported seem to emphasize the necessity of using caution in drawing conclusions regarding the blood-flow through an organ from determinations of its changes in volume.

SUMMARY

Stimulation of the splanchnic nerve produces changes in the distribution of the blood that permit of the following conclusions:

1. The blood-pressure in the femoral vein shows an average increase of 0.96 mm. Hg from stimulation for forty seconds. The phases of increase and final return to normal closely agree with similar changes in the general pressure.

2. An average increase of 1.8 mm. Hg was obtained in the external jugular vein by stimulation for thirty seconds.

3. In the pancreatic and renal veins a fall in pressure results, which is usually small and variable in character. A few determinations in the inferior and superior vena cava indicate slight changes in the pressure.

4. The measurements of the blood-flow in the external jugular vein show an increase of 12.5 per cent. Estimated from the normal flow this gives for the two jugular veins a compensatory flow of 34.4 cc. per minute.

5. The blood-flow in the femoral vein showed an increase of 15 per cent. The estimated compensatory flow in this case gave a value for the two posterior extremities of 15.3 cc. per minute.

6. If we assume that the circulation of the anterior extremities affords an accelerated flow approximately equal to that of the posterior extremities, then the increased transfer of blood permitted by the vascular circuits of the head and extremities together is sufficient to compensate for the diminished flow through the portal circuit.

7. There is no indication in either the readings of venous pressure or the stromuhr records from the jugular and femoral veins of a change in flow coincident with the second phase in the rise of the general blood-pressure.

8. The denervated kidney showed a correlation between its relative volume and the quantity of blood flowing through it. There was a temporary increase in flow coincident with the initial increase in volume, and a marked decrease in the flow corresponding to the similar change in the volume.

9. A change in the volume of an organ is not an infallible criterion of the relative quantity of blood flowing through it.

I wish to express my sincerest thanks to Prof. Frederic S. Lee for his kind advice and criticism. I have much pleasure also in thanking Prof. R. Burton-Opitz for suggesting the problem and for invaluable help he has given me throughout the work.

THE INDEPENDENCE OF THE LOBES OF THE LIVER

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Our general conception of the human liver is that it is one large gland, uniform throughout in structure and in function. Considerable evidence is available to show however that this is not altogether true, and that there is both an anatomical and a physiological independence of the two main lobes, the right and the left lobes.

The anatomical independence consists in a separation of the biliary and the vascular systems of the right lobe from those of the left lobe, the true division between the lobes being a hypothetical plane drawn between the gall bladder and the fossa of the inferior vena cava. The physiological independence of the two lobes is directly dependent upon the fact that the blood flowing from the various portal radicles into the main portal vein, does not mix diffusely, but streams along in thread-like currents, each retaining its individuality for distances ranging from three to eight centimeters. Depending upon this principle of blood flow we have shown that in the dog, the blood from the stomach, spleen, duodenum and part of the jejunum, and also from the rectum, flows principally to the left and central portions of the liver, while the blood from the lower jejunum, the ileum, and the first three-fourths of the large intestine, flows in greatest amounts to the right and central lobes.

The importance of such a streaming of blood in the portal vein is worthy of consideration and study in the diagnosis and treatment of surgical and medical disturbances of the liver with their possible associated gastro-intestinal lesions. Glenard[1] in 1890

[1] Glenard, F. Du Foie Chez les Diabétiques, Lyon Medical, 1890 (64), pp. 5–18, 80–89, 115–127, 189–198, 259–265.

published the results of his clinical studies by 'pouce' of the lower border of the liver, in diseases such as diabetes, gastritis, and biliary lithiasis, which showed that definite alterations occurred in size, tenderness, and consistency of the lower palpable border of the liver. In diabetes he found the right lobe to be the seat of the most marked changes; in gastritis from alcoholism, the left lobe was most involved; in biliary trouble, the central portion was principally changed.

The present anatomical division of the adult human liver by the ligamentum teres hepatis, though convenient, is untrue, and not based upon embryonal development. The ligamentum teres hepatis is the remains of the left umbilical vein, the right one of which is situated, in early embryonal life, an equal distance to the right of the gall bladder. The gall bladder is the true center of the liver, both in the embryo and in the adult. Rex,[2] Fowler,[3] and Bradley[4] working separately upon the embryological development of the liver in a series of animals closely associated to man in the phylogenetic scale have shown that the primitive divisions of the liver have disappeared, leaving only superficial demarcating lines.

Rex and Fowler find that there are primarily six lobes, which correspond to Bradley's three lobes as follows:

Rex, Fowler	*Bradley*
Right lateral, Caudate, Spigels	Right
Right central, Left central	Central
Left lateral	Left

Brochet[5] emphasized that the liver cells grew out along the omphalomesenteric and umbilical veins, governing the development and to

[2] Rex, Hugo. Beiträge zur Morphologie der Säugerleber. Morphologisches Jahrbuch, 1888.

[3] Fowler, Cited by Bradley.

[4] Bradley, C. C. Contribution to the Morphology and Development of the Mammalian Liver. Journal of Anatomy and Physiology, 1908 (43), 1–42.

[5] Brochet, Cited by Bradley (loc. cit.).

some extent the shape of the liver. It is a well known fact that in human embryos, at the end of the second week, the hepatic bud of gut endothelium invades the omphalomesenteric veins which break up into sinusoids of a complex capillary nature. At about this time the umbilical veins begin to develop, the right one of which is more aborescent and larger at first, thus affording an earlier development of the right lobe. The right umbilical vein soon becomes smaller while the left umbilical vein gets larger and becomes imbedded in its fissure. Bradley has clearly shown that the gall bladder, the cystic duct, and the original meso-gastric attachment, are along a line midway between the two umbilical veins. The liver of the pig has originally three lobes, the central one of which is bounded on either side by an umbilical vein; the gall bladder occupies the central position. After the twenty-fifth day there is but the left umbilical vein remaining imbedded in the deep hepatic fissure. Finally by a complex process of atrophy of parts of both omphalomesenteric veins, and a fusion of other parts, the common portal vein is formed.

Wertheimer and Le Page[6] showed the independence of the bile ducts and capillaries of the right lobe from those of the left lobe by demonstrating spectroscopically the absence of any trace of cow's bile in either lobe after injecting the duct of the opposite lobe with cow's bile. Looten[7] repeated the experiment on 25 cadavers, using indigotate of sodium. He could demonstrate no intra-hepatic capillary connections between the bile ducts of the two sides. From the injection of water and of methylene blue into one of the portal branches entering the liver, Séregé[8] found the corresponding lobe to be swelled up and tense, while the opposite lobe remained flaccid; the line of division was in a plane between the gall bladder and the fossa of the inferior vena cava. If the left branch of the portal vein was injected, swelling of the quadrate lobe accompanied swelling of the left lobe, while injection of the right branch caused simultaneous swelling of the

[6] Wertheimer, E. and Le Page, L. Sur les voies de résorption de la bile dans le foie. Comp. Rend. de la Soc. de biol. Par. 1896, (10), 950.

[7] Looten, J. Contribution à l'étude de l,'independance vasculaire du foie droit et du foie gauche. J. de l'anat. et de la phys. nor. et path., 1908 (87), 110.

[8] Séregé, H. Contribution à l'étude de la circulation du sang porté dans le foie et des localizationes lobaires hépatiques. Jour. de Med. de Bordeaux, 1901 (31), 271-75, 291-95, 312-14.

right, Spigelian, and caudate lobes. Gilbert and Villaret,[9] Brissaut and Bauer[10] and others, repeating the above experiments confirmed that there is a gross independence of the vascular systems of the two lobes, but deny an absence of capillary anastomoses in the median plane.

Division of the liver in a plane lying between the gall bladder and the inferior vena cava produces two parts which approximate each other very closely in weight. The present shape of the liver is entirely misleading and is supposedly due to: (*a*) the shape and contents of the gastro-intestinal tract (Deuverony); (*b*) the position and mode of fixation of the liver together with the difference in the shape of the thorax and abdomen (Kieth); (*c*) the modification in the form of the trunk and the flattening of the dome of the diaphragm (Ruge).

Thrombosis of the left or the right portal branches produces atrophy respectively of the left and quadrate, or of the right and Spigels' lobe. The atrophy for instance, due to complete thrombosis of the right portal branch and the right hepatic artery never quite reaches this hypothetical dividing plane, proving the existence of a capillary overlapping in this central region. It is along this central plane where rupture of the liver most frequently occurs, probably because of the absence of large blood vessels and bile ducts; ruptures here are surgically known to be much better tolerated than ruptures elsewhere in the liver, this being due no doubt to its double venous and arterial blood supply. It is then quite definitely established that there is at least a gross anatomical independence of the vascular and of the biliary systems of the two main liver lobes. Any small branch of the portal vein if injected separately causes a swelling of a corresponding region of the liver, which fact may be considered a segmental independence from the adjoining portions.

It was the intention of our work to determine definitely if possible whether or not, and to what extent, the smaller streams of blood from the veins of the various regions of the gastro-intes-

[9] Gilbert, A. and Villaret, M. Researches sur la circulation du lobule hépatique. Arch. de Med. Experimentale. 1909 (21), 373–442.

[10] Brissaut, E. and Bauer, A. L'independance des lobes du foie est une Hypothese. Jour. de l'Anatomie, 1909 (45).

tinal tract, maintained their individuality as distinct currents after their confluence to form the stream in the common portal vein. This principle of partially retained individuality of confluent liquids is proportionately sharper the greater the viscosity of the fluids. It is a well known observation that a river, when formed by the junction of a muddy with a clear stream, will remain half muddy and half clear for long distances. Not infrequently the drinking water of towns on one side of a large river escapes contamination with pathogenic bacteria, while on the opposite bank the cities deriving their water supply from the same source have become the seats of epidemics due to the emptying of sewerage into their side of the river farther up stream. The microscopic examination of capillaries in the web of a foot of a live frog demonstrates the comparative retention of individuality of very small streams of blood coming together. Of still greater pertinence is the confinement to definite courses in the right auricle of the foetus of the inflowing streams from the superior and inferior vena cavas. The importance of this principle in the maintenance of the physiological independence of the two main lobes of the liver is paramount.

In 1901 Séregé[11] by injecting India ink into the splenic vein found particles of the ink in the left lobe only, one hour later; if a radicle of the large mesenteric vein were injected, the particles were found only in the right lobe. Objection to the use of India ink for such an experiment is quite manifest because it is entirely foreign in its physical character to that of the portal blood. Glenard[12] and Silvestri[13] confirmed the above experiments but Gilbert and Villaret, Pincherel, Brissaut and Bower, Looten, and others all found an equal distribution of the ink particles throughout the liver, when either the splenic or the large mesenteric vein was injected. In 1902 Séregé[14] determined the

[11] Séregé, H., loc. cit.

[12] Glenard, F. Notes sur les Localizations Lobaires Hépatiques. Bull. d. l. soc. Med. des Hosp. 1901 (18), 386-97.

[13] Silvestri. Sull independenza funzionale e anatomica dei lobi dell figato. Gazetta delgi ospedali. Milano. 1905 (24), 570-72.

[14] Séregé, H. Sur la teneur en ureé de chaque lobe du foie en rapport avec les phases de la digestion. Comp. Rend. Hebd. Soc. de Biol. Par. 1902 (14), 200-202.

amount of urea in the right and the left liver lobes respectively, 2, 4, 6, and 8 hours after ingestion of 500 grams of finely chopped meat by dogs previously starved for 24 hours, and found that for the first two hours the urea content was greater in the left lobe; that at the fourth hour the right lobe contained more than the left; that at the sixth hour the right lobe still contained more urea than the left; that at the eighth hour, approximately at the termination of digestion, the urea content was equal in both sides. The conclusion reached was that as the food passed down the intestinal tract, absorption from the various segments increased the urea content first on the left and then on the right side of the liver, because of a double blood current in the portal vein. Variation in the glycogenic and the iron content of the two lobes during the different phases of digestion and differences in toxicity of extracts of the two lobes to small animals, have all been reported. Loeb[15] in 1907 regularly found more iodine in the right lobe of rabbits, than in the left lobe one hour after a 0.9 gram subcutaneous injection of potassium iodide, and the analyses of similar material by Wells and Hedenburg,[16] gave results generally agreeing with this statement.

EXPERIMENTAL

Our experiments consist, (1) in the injection of fat emboli in the various radicles of the portal vein with a subsequent determination of their location and lodgment in the liver, (2) in the injection of dilute copper sulphate solutions into the lumen of the gut at various places, permitting normal absorption to go on over periods of from five days to three weeks, with a final quantitative determination of the copper in the different lobes of the liver.

Fat Injections: The dogs were anaesthetized with ether, the abdomen opened, and the various veins injected with from 2 to 4 cc. of an emulsion of olive oil in blood plasma. The veins were always injected without disturbing their normal position. The emulsion was made fresh immediately before each injection by vigorously shak-

[15] Loeb, O. Independence in function of the liver lobes. Arch. exp. Path. und Pharm. 1907, 56, 321.

[16] Wells, H. G. and Hedenburg, O. F. Jour. Inf. Diseases, 1912 (11), 349.

ing one part of olive oil to eight parts of defibrinated blood drawn from the femoral vein. This produces an emulsion not varying to any appreciable extent in viscosity or specific gravity from normal portal blood. The injections were made as soon as the finer air bubbles arose from the emulsion; the syringe was always held with the needle downward, so that the large coalesced fat globules would rise to the surface and escape injection. Injections were made slowly, requiring from one-half to one minute so as to simulate as near as possible, the normal venous flow. Immediately following the injections, the dogs were bled to death from their jugular veins. Two pieces of liver tissue were taken from each of the six lobes of the liver, one piece from the upper third and the other from the lower third of each lobe. The reason for this lies in the discovery that a single block of tissue from any one lobe is not representative of the number of emboli in that lobe; the lower portions of a lobe might contain one-third or one-half again as many emboli as the upper third. The average number of emboli in sections taken from four different parts of the two left lobes, is quite constantly representative of these two lobes The same applies to the two central and to the two right lobes. The blocks thus taken, as soon as the dog was bled to death, were placed in 10 per cent formalin and when thoroughly hardened, cut on a freezing microtome. Six sections from each block were stained with Sudan III, and mounted in glycerine in the usual manner. For each lobe of the liver there were finally two slides of four to six sections each.

Examination of Microscopical Sections: Precaution was taken in the microscopical determination of the amount of fat, to select sections for comparison that were of equal thickness, for it is obvious that a thick section will contain more fat emboli that a thin section. The emboli were contained mainly in the interlobular portal venules, and to a lesser extent in the hepatic sinuses, rarely in the central veins. By repeated low power examinations of the equally thick sections of the various lobes it is not difficult to note even slight differences in the amount and number of fat emboli. The amount of fat can be designated only in terms of comparative meaning, as compiled in table I.

Copper Injections: Injections of a weak solution of copper sulphate twice daily during periods varying from five days to three weeks, were made into the lumen of various segments of the intestine; absorption under these conditions is identical to the absorption of food from the intestines. Those dogs injected subcutaneously received 2 to 3 cc. of a one per cent copper sulphate solution every other day. Injections into the segments of the jejunum and ileum were made possible

by the production of Thiry-Vella fistulas, composed of loops of gut from eight to twelve inches long, both ends of which were sewed to the skin; the lumen of the intestine was restored and the animals lived for an indefinite period. In the production of the loops extreme care was taken not to disturb the normal position of the gut or of the mesenteric veins, especially those veins coming from the loop.

Determination of Copper: Determination of the copper was made by the colorimetric method. In dogs 9, 10, 13, 14, 15 and 16, several samples of each lobe were taken and the copper in them estimated separately, while in dogs 11, 12 and 17, the whole lobe was ground up, thoroughly mixed and a 10-gram sample taken.

All chemicals used in the analyses were chemically pure and copper free. Approximately 10-gram samples of tissue were analyzed. The tissue was charred with 10 cc. of concentrated sulphuric acid and then heated on an air bath in a Kjeldahl flask with frequent additions of a few cubic centimeters of concentrated nitric acid until perfectly clear, and finally until the sulphuric acid solution had been evaporated down to 5 or 8 cc. The resultant liquid was neutralized (to litmus) with a strong solution of sodium hydroxide (mit alkohol gereinigt) and acidified with 1 to 2 cc. sulphuric acid (diluted one-half with water). The copper in this solution was deposited on a platinum electrode by means of a suitable current previously tested out, passed for a period of from seven to eight hours. After the completion of the electrolysis the electrode was washed with distilled water (copper free) and finally with alcohol while the current was still on. The copper on the electrode was dissolved in several centimeters of concentrated nitric acid which was subsequently evaporated on a water bath, leaving the copper as nitrate. To the copper nitrate was added for dissolving, this solution, or parts thereof, being compared to a standard copper nitrate solution containing $\frac{1}{4}$ cc. acetic acid (1-10) and 10 cc. of distilled water, the same amount of acetic acid. To both solutions (the known and the unknown) was now added 1 cc. of a 50 per cent ammonium nitrate solution, and 1 cc. of a 4 per cent freshly prepared potassium ferro-cyanide solution. Comparisons were made in a Dubosque colorimeter. The important considerations were to get the two solutions for comparison as nearly equal in copper concentration as possible by dilution, to have the same amount of acetic acid present in each and to make the readings rapidly.[17] (See Table II.)

[17] This method of determining copper in tissues will be given in more detail in a future paper on "The Chemotherapy of Tuberculosis by means of Copper," to be published by H. J. Corper.

TABLE I

Right lobe

DOG	VEIN INJECTED	A	B	C	D
1	Splenic	X++	X−−	X−−	X−−
2	Duojejunal	X+	X++	X	X+
3	Jejunal	X+	X−	X−	X−−
4	Ileo-jejunal	X+	X++	X+	X++
5	Ileo-jejunal	X+++	X+++	X−−	X−−
6	Ileal	X+	X++	X+	X+
7	Rectal	X+++	X−	X−	X−
8	Rectal	X	X++	X+	X+++

Central lobe

1	Splenic	X+++	X+	X+++	X
2	Duojejunal	X+++	X+	X	X+
3	Jejunal	X++++	X++	X++++	X+++++
4	Ileo-jejunal	X++	X++	X	X+
5	Ileo-jejunal	X+	X	X+	X
6	Ileal	X−	X+	X+	X+
7	Rectal	X−	X+	X	X−
8	Rectal	X++	X++	X	X−

Left lobe

1	Splenic	X++	X+++	X+++	X++++
2	Duojejunal	X++	X++	X+	X++
3	Jejunal	X+++++	X++++	X++	X+++
4	Ileo-jejunal	X++	X++	X++	X++++
5	Ileo-jejunal	X	X	X−	X
6	Ileal	X	X+	X	X
7	Rectal	X+++	X++	X++	X++
8	Rectal	X++++	X++	X	X++++

Embolic fat in the liver after injecting the various veins tributary to the portal vein. A, B, C, and D, of each lobe indicates the place in each lobe from which sections were taken for study (see fig. 1).

In the above table, "X" represents a certain quantity of number or fat emboli which is approximately one embolus to every other lobule. In sections marked "X−−" there is practically no fat, or at most but one or two emboli in the entire section. In sections marked "X+" there is a barely appreciable increase of fat emboli over "X" number. In sections with two and three times "X" number of emboli, the respective symbols, "X++" to "X+++++" are used.

TABLE II

DOG	PART INJECTED	RIGHT LOBE	CENTRAL LOBE	LEFT LOBE
9	Subcutaneous (2 weeks)	0.374		0.39
10	Subcutaneous (2 weeks)	0.151		0.173
11	Jejunum (1 week)	0.3619	0.3525	0.4348
12	Ileum (1 week)	0.5582	0.4002	0.3468
13	Jejunum (1 week)	0.51		0.708
		0.62		0.818
14	Ileo-jejunal junction (2 weeks)	0.999		1.47
		1.15		1.45
15	Rectum (3 weeks)	0.382		0.474
16	Rectum (5 days)	0.82		0.95
17	Rectum (1 week)	0.147	0.3078	0.3899

Representing milligrams of copper each 10 grams of liver tissue.

Interpretation and Discussion: It is seen from the protocols of fat injections that: (A), emboli introduced into the splenic (1), small mesenteric (8 and 9), and veins from the upper jejunum and duodenum (3 and 6), lodge mainly in the left and central lobes of the liver; (B), emboli injected into the lower jejunum (5), and ileum (6), lodge principally in the right and central lobes. In dog 1, there is practically no fat in the right lobe; it will be noticed in figure 1 that the splenic vein enters at a right angle on the extreme left side of the portal vein. In dog 2, the left liver lobes are but slightly favored; the vein from the duojejunal region it will be noticed enters behind and almost in the center of the portal vein. In dog 3, the right lobe is quite free from emboli while the left and central lobes contain a great many; here the vein (*f* of fig. 1), enters to the extreme left border of the portal vein. In dog 5, there is approximately an equal distribution of the fat in all lobes, while in dog 6, the right lobes are appreciably favored; in dog 6, the veins (*g* of fig. 1) were injected, which empty into the right border of the portal vein. In dogs 7 and 8, the left lobe is definitely the seat of the larger number of fat emboli, while the central and right lobes contain approximately an equal and smaller amount. In dogs the left lobes are the largest, the central next and the right lobes smallest; hence slightly more blood would flow to the left lobes than to the right, a fact which

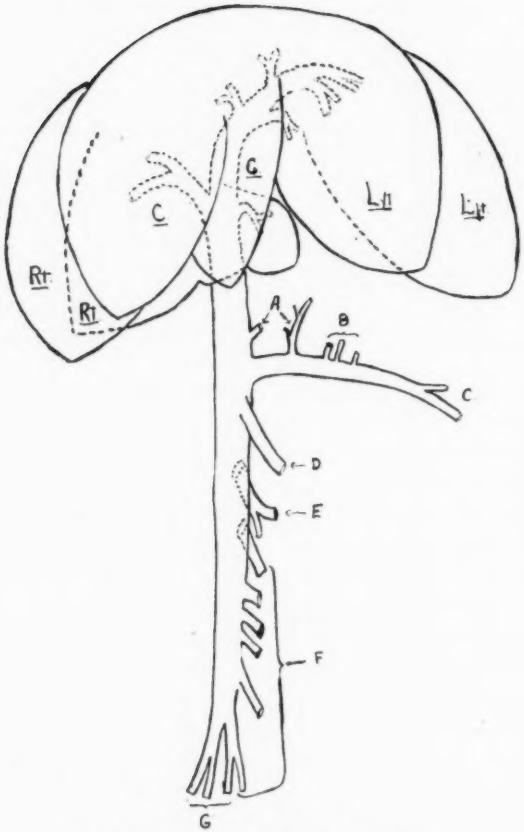

FIG. 1. PORTAL SYSTEM OF A DOG.

Showing the exact angle and side of entrance of each portal tributary. (*A* and *B*) veins from pancreas and stomach; (*C*) splenic vein; (*D*) small mesenteric vein; (*E*) duodenal and pancreatic veins; (*F*) jejunal vein; (*G*) vein from ileum and ascending colon.

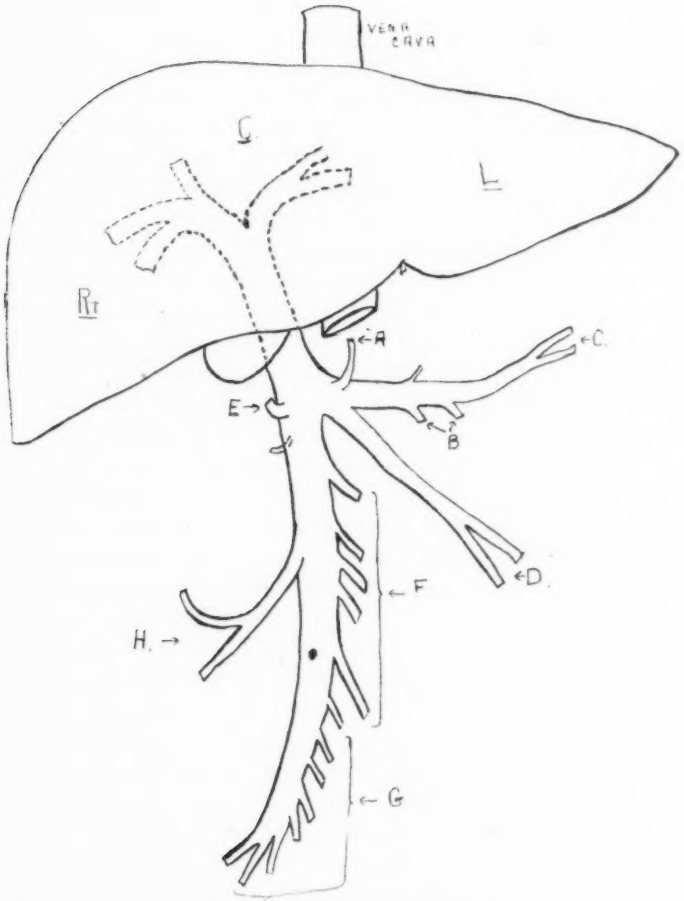

FIG. 2. PORTAL SYSTEM OF MAN.

Showing the exact angle and point of entrance of each portal tributary. (*A*) from lesser curvature of stomach; (*B*) pancreatic veins; (*C*) splenic veins; (*D*) small mesenteric vein; (*E*) from the greater curvature of stomach; (*F*) jejunal veins; (*G*) ileal veins; (*H*) vein from ascending colon.

even of some importance is not sufficient to explain the above distribution of the emboli.

Referring to table II and comparing the results with table I, it is found that similar results are obtained, namely that copper being absorbed through the jejunal and rectal veins is deposited more in the left lobes, while copper absorbed from the gut through the ileo and ileo-jejunal veins is carried in largest amounts to the right lobes. Where the copper has been determined in the central lobes it is always found to be intermediate in quantity between the amount found in the left and in the right lobes.

The variation in the amount of fat and copper in the different lobes is due to some regulating mechanism which undoubtedly is dependent upon the physical situation and angles of the venous radicles from the various gastro-intestinal regions. The blood flowing through the splenic vein does not mix diffusely with the blood in the portal vein, but streams along as an independent current in the left half of the portal vein. The blood coming in through the ileal veins (*g*, fig. 1) keeps in a somewhat individual course along the right border of the portal vein, but having to flow twice as far as the streams from the splenic and jejunal veins to reach the upper portion of the portal vein it mixes more with the other incoming streams and consequently becomes less an independent and individual current. This is shown in our tables by the fact that, though the fat from the ileal veins goes to the right lobe mainly, it is not so completely carried there as the fat, which injected into the splenic vein, is carried to the right lobe.

The physiological independence of the two sides of the liver is not sharp and entirely distinct, but overlapping; this is due to the mixing and diffusion of the currents. This blending is dependent upon and proportional to the viscosity of the fluids, the angles of the course, the velocity of the merging streams, and to the distance of the flow.

The subcutaneous injections were made to determine whether the two sides of the liver absorbed and retained the same amount of copper per unit weight when the copper was introduced into the general blood system. In dogs (9 and 10) the left lobe is favored to an extent which though slight, cannot be attributed to

observational error. Loeb constantly found more iodine in the right lobe of rabbits an hour after the subcutaneous injection of 0.9 gram of potassium iodide. Séregé found more iron and glycogen in the left lobes of starving dogs, the iron being of larger amounts in the left lobe he supposed, because of the hemolytic action of the spleen on injured corpuscles. It is possible that the rapidity of the blood currents to the right and the left lobes may account for this difference in content of glycogen, iron and copper, though such a difference in current has not yet been demonstrated satisfactorily.

We have searched several thousand autopsy records to find practical expression of the physiological independence of the lobes of the liver, and we have reviewed the chief works on liver abscesses, emboli, and thrombosis, yet have found no definite conclusive instance wherein lesions of the liver are shown to be associated with gastro-intestinal regions, so as to be indicative of an independence of the currents in the portal vein. This negative result is due to the facts that (*a*), no attempt has been made at necropses to accurately describe the locations of liver lesions and their correlated intestinal lesions, (*b*), an insufficient number of necropses have been performed with the idea in mind of a physiological association of the lobes of the liver with their intestinal segments, (*c*), the true division of the liver into right and left lobes in a plane between the gall bladder and the inferior vena cava has not been generally known and accepted, the ligamentum teres hepatis having been held as the anatomical division. The clinical observations of Glenard in 1890 on gastritis with its associated tender and swollen left liver lobe, and on diabetes with its associated hypertrophied right lobe, are in accord with our results. By comparing the diagram of the portal system in the dog with that in man (fig. 2), it is evident that a great similarity of structure is present, and that what has been found to be true concerning an independent streaming of the blood in the portal vein, with a segmental association of the gastro-intestinal tract with definite regions of the liver in the dog, may be applied with propriety to the portal system of man; it is dependent upon the principles of physics governing the confluence of fluids in closed channels.

CONCLUSIONS

Our experiments show that there is a physiological independence of the lobes of the liver in dogs, depending upon the fact that the blood flowing into the portal vein from each of the smaller veins of the portal system does not blend diffusely into a common current, but remains individualized to a considerable degree, streaming in thread-like currents, for distances varying up to 10 cm.

Depending upon this principle it is found by injection of emulsified fat in the various portal tributaries, and by the absorption of copper from the various isolated intestinal segments, that: (1) the blood from the stomach, spleen, duodenum, first part of the jejunum, and from the rectum, flows mainly to the left lobes of the dogs liver and least to the right lobes; (2) blood from the lower jejunum, ileum, and first part of the large intestine, flows principally to the right lobes of the liver and least to the left lobes; (3) this independence is not entire, but overlapping, due to an intermixing of the portal currents; (4) the currents of blood from the splenic and rectal veins, are, at the hilus of the liver, more sharply defined than the currents of blood from the ileal veins which must flow a greater distance in the portal vein to reach the hilus of the liver, and consequently become more mixed and less independent.

THE VISCOSITY OF LAKED BLOOD

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It has recently been stated by Adam[1] that laked blood possesses a greater viscosity than "living" blood, this conclusion being based in large part upon the determinations made some years previously by Determann.[2] While no reference has been made in this paper to very similar tests which I completed during the autumn of 1903, I may be permitted to deal with this problem again at somewhat greater length than was thought necessary at that time, because the experiments just referred to have led to results which are not in agreement with mine.[3]

My early determinations were made with defibrinated ox-blood which had been frozen and thawed eight times in succession. In view of the fact that the coefficients obtained under these conditions showed very decided and regular variations, I feel justified in attributing the discrepancy in our results to differences in the methods of preparing the laked blood. At the same time I must admit that a direct comparison of our results may not be permissible, because while my determinations have been made with defibrinated blood, Determann has employed human blood kept fluid by means of hirudin. The blood collected by him in this manner was frozen and thawed "repeatedly." It will be shown subsequently that the results actually depend upon the number of times the blood is subjected to this process and that the difference in our results is directly attributable to

[1] Zeitschr. f. klin. Med., lxviii, 187, 1909.

[2] Zeitschr. f. klin. Med., lix, 203, 1906.

[3] Proc. of the Society of Exp. Biology and Medicine, 1903; also Pflüger's Archiv, cxix, 366, 1907.

the fact that the blood tested by me has been frozen oftener than that employed by Determann.

The following procedure has been adhered to in the present experiments. Having determined the viscosity of the defibrinated blood, a sufficient quantity of it was placed in a small ice-cream freezer and rapidly frozen by adding sodium and calcium chloride to the ice in the surrounding receptacle. In Experiment 1 the freezing was accomplished with much greater speed than in Experiment 2. Having solidified the blood completely, the metal box containing it was placed in warm water until its contents again became perfectly fluid. This procedure was repeated eight times in all cases. Samples of blood were withdrawn after the first, second, fourth, sixth and eighth freezing. The tests embodied in Experiment 3 were made with defibrinated blood which had been frozen very slowly in the ice-house, about twelve hours being required for each freezing. The viscosimeter made use of in these determinations possesses the same general features as the one employed by me for earlier tests of this kind.[4] The diameter of the capillary measured 4.1 mm. and its length 29 cm. The experiments were made at a temperature of 37°C.

The data given in tables 1, 2, and 3 show very clearly that defibrinated blood which has been rendered laky by freezing it eight times in succession, possesses a slighter viscosity than the original blood. In table 4 the coefficients indicating this fact have been arranged in a manner permitting an easy comparison with the viscosity of distilled water at 37°C., the coefficient of which is 4700. In the first of the present experiments the viscosity has been reduced from 885.6 to 1106.5; in the second from 839.7 to 952.1, and in the third from 839.7 to 1067.8. As these results are very decisive and agree perfectly with those published by me at an earlier date, I feel justified in regarding this question as having been satisfactorily settled.

It has been shown by me that the viscosity of defibrinated blood is somewhat less than that of the normal circulating blood;[5]

[4] Pflüger's Archiv, lxxxii, 447, 1900.
[5] Pflüger's Archiv, lxxxii, 446, 1900.

TABLE 1

Viscosity of laked blood. Experiment 1.

			DETERM.	SPECIFIC GRAVITY	QUANTITY	TIME	PRESSURE	COEFFICIENT OF VISCOSITY	DIFFERENCE	AVERAGE VALUE OF VISCOSITY	GREATEST DIFFERENCES
			no.		*mg.*	*sec.*	*mm. Hg.*				
Defibr. Blood	Normal		1	1.0557	781.4	54.80	156.8	884.1	3.1	885.6	+ 41.6
			2	1.0557	764.0	53.46	156.6	887.2			
	Frozen	once	1	1.0529	825.2	59.40	159.3	850.0	12.0	844.0	+ 88.4
			2	1.0529	793.0	57.68	159.9	838.0			
		twice	1	1.0519	600.0	48.48	159.3	758.1	5.0	755.6	− 206.2
			2	1.0519	653.5	53.28	158.9	753.1			
		four times	1	1.0529	600.5	38.51	158.2	960.8	2.1	961.8	− 144.7
			2	1.0529	800.3	51.55	157.2	962.9			
		eight times	1	1046.1	620.3	35.86	155.0	1094.8	23.5	1106.5	− 220.9
			2	1046.1	1006.2	58.73	150.3	1118.3			

TABLE 2

Viscosity of laked blood. Experiment 2.

			DETERM.	SPECIFIC GRAVITY	QUANTITY	TIME	PRESSURE	COEFFICIENT OF VISCOSITY	DIFFERENCE	AVERAGE VALUE OF VISCOSITY	GREATEST DIFFERENCES
			no.		*mg.*	*sec.*	*mm. Hg.*				
Defibr. Blood....	Normal		1	1.0549	555.0	43.95	147.8	831.2	17.1	839.7	
			2	1.0549	756.6	59.35	146.2	848.3			+ 99.6
		twice	1	1.0523	628.2	55.93	150.1	729.8	20.6	740.1	
			2	1.0523	548.2	48.03	148.3	750.4			− 51.1
		four times	1	1.0516	637.5	50.49	155.1	794.5	6.5	791.2	− 112.4
			2	1.0516	696.0	56.64	152.2	788.0			
	Frozen										− 19.3
		six times	1	1.0515	655.8	54.18	145.5	812.0	3.0	810.5	
			2	1.0515	692.8	58.13	143.6	809.0			− 141.6
		eight times	1	1.0490	711.6	47.10	156.1	947.0	10.2	952.1	
			2	1.0490	864.0	54.70	154.2	957.2			

TABLE 3

Viscosity of the laked blood. Experiment 3.

			DETERM.	SPECIFIC GRAVITY	QUANTITY	TIME	PRESSURE	COEFFICIENT OF VISCOSITY	DIFFERENCE	AVERAGE VALUE OF VISCOSITY	GREATEST DIFFERENCES	
			no.		*mg.*	*sec.*	*mm. Hg.*					
Defibr. Blood	Normal		1	1.0549	555.0	43.95	147.8	831.2	17.1	839.7	+ 288.3	− 228.1
			2	1.0549	756.6	59.35	146.2	848.3				
	Frozen	twice	1	1.0537	334.2	54.04	111.6	539.7	23.5	551.4	−178.9	
			2	1.0537	294.9	46.45	109.8	563.2				
		four times	1	1.0535	439.5	55.25	107.0	724.2	12.2	730.3	− 157.6	
			2	1.0535	453.7	56.20	106.8	736.4				
		six times	1	1.0545	468.6	54.32	95.9	875.5	24.8	887.9	− 179.9	
			2	1.0545	472.7	53.62	95.3	900.3				
		eight times	1	1.0533	595.6	44.60	123.7	1054.9	25.8	1067.8		
			2	1.0533	689.1	51.03	122.1	1080.7				

TABLE 4.

	EXPERIMENT	COEFFICIENTS OF		π COMP. WITH DIST. WATER AT 37°C.	
		Normal blood	Laked blood	Normal blood	Laked blood
Earlier tests	1	665.7	982.3	7.0	4.7
	2	634.7	1041.9	7.4	4.5
	3	622.2	825.8	7.5	5.6
Present tests	4	885.6	1106.5	5.3	4.2
	5	839.7	952.1	5.6	4.9
	6	839.7	1067.8	5.6	4.4

the average difference in the coefficients before and after defibrination amounting to 117 points. If an allowance is made for this in the determinations now under discussion, it will be seen that blood which has been treated in the manner here described, possesses a viscous resistance which is not only markedly below that of defibrinated, but also much below that of normal blood.

The experiments at hand also prove that defibrinated blood which has been rendered laky by repeated freezing, does not become less viscous from the beginning, but assumes at first a somewhat greater viscosity. Only if the freezing is repeated a great number of times does the reduction in the viscosity become unmistakable. The turning point seems to lie at about the second freezing, i.e., defibrinated blood which has been frozen three times clearly shows a lesser inner friction than that possessed by the original sample. For example, the coefficient of the normal blood used for Experiment 1 amounts to 885.6 which fact implies that this blood possesses a viscosity about 5.3 times greater than that of distilled water at 37°C. After the second freezing the coefficient shows the numerical value of 755.6 and hence a viscosity 6.2 times greater than that of distilled water. After the fourth freezing K equals the value 961.8 and after the eighth freezing the value 1106.5. A decrease in the viscosity has therefore taken place from 885.6 to 961.8 and 1106.5, respectively. The defibrinated blood which previously possessed a viscous resistance 5.3 times greater than that of distilled water at 37°C., now exhibits one only 4.8 and 4.2 times greater. In this case

the viscosity of the circulating blood may be assumed to have been about six times greater than that of distilled water at 37°C.

In order to prevent coagulation Determann and Adam were obliged to add new amounts of hirudin to the blood after each freezing. On standing the laked blood became more viscous until finally the agglutination of the stromata made further determinations difficult. When centrifuged, the blood separated into two layers, namely, into an upper, supposedly cell-free stratum showing a viscosity only slightly greater than that of the living blood, and a lower layer, which being densely packed with stromata, possessed an inner friction so high that it could scarcely be determined. Both authors state that the viscosity pursues a course parallel to the haemoglobin content of the blood; in fact, Determann believes that the red corpuscles contain highly viscous substances which are responsible for the greater viscosity of laked blood. During the time that these substances remain deposited within these cells, they are unable to exert their influence, but when the corpuscles are ruptured and their contents are freely discharged into the surrounding medium, the total viscosity of the blood is raised in a very definite measure.

This explanation is well substantiated by the present experiments. When, however, the blood is frozen a great number of times (5 to 8), many of the red cells become thoroughly agglutinated and eventually collect as a rather heavy deposit upon the bottom and sides of the receptacle. The present determinations which have shown that the viscosity of defibrinated blood frozen eight times in succession is decidedly less than that of normal blood, have been made with the liquid portion of the blood which is relatively free from clumped cells. I gladly admit, however, that laked blood which has been recharged artificially with all the stromata deposited upon the walls of the receptacle, must possess a high viscosity, but blood of this type cannot be properly tested, because it would effectively block any capillary of the size ordinarily employed for these determinations.

The gradual reduction of the specific gravity betrays a loss of some of the constituents of the normal blood. In general this quality of the blood pursues a course parallel to the viscosity;

at first, however, a lower specific gravity is associated with a higher viscous resistance. This fact indicates that these two properties of the blood are not always directly related and that a low specific gravity may be encountered together with a high viscosity.

STUDIES ON THE VASOMOTOR CENTRE: THE EFFECTS OF HEMORRHAGE AND REINJECTION OF BLOOD AND SALINE SOLUTION[1]

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INTRODUCTION

The withdrawal of blood might be expected to stimulate the vasomotor centre as a conservative measure. The following experiments bring direct evidence for this anemic stimulation, but they also show that it is limited, and that excessive hemorrhage depresses, and if prolonged, paralyzes the centre. They show, further, that this depression can be relieved by the prompt injection of blood or saline solution; but that these are ineffective if the paralysis has been permitted to go too far.

Method. The reactions of the vasomotor centre were studied by perfusion of the spleen.[2] Dogs were used exclusively. The blood was withdrawn from the femoral artery in successive portions of 5 to 20 cc. per kilogram, repeated until the blood pressure was reduced to the "shock level" of 30 to 50 mm. In certain experiments the defibrinated blood was then reinjected.

The typical effects of progressive hemorrhage on the vasomotor centre (fig. I). Soon after the hemorrhage is started, and when the loss of blood is still small, the vessels begin to constrict. As the hemorrhage proceeds, the constriction becomes more and more pronounced, and then gradually passes into progressive dilation, which eventually becomes constant. The vasoconstric-

[1] A preliminary report was published in the Journ. Pharm. and Exp. Therap., 1910, i: 571.

[2] Sollmann and Pilcher: This Journal 1910, xxvi: 233.

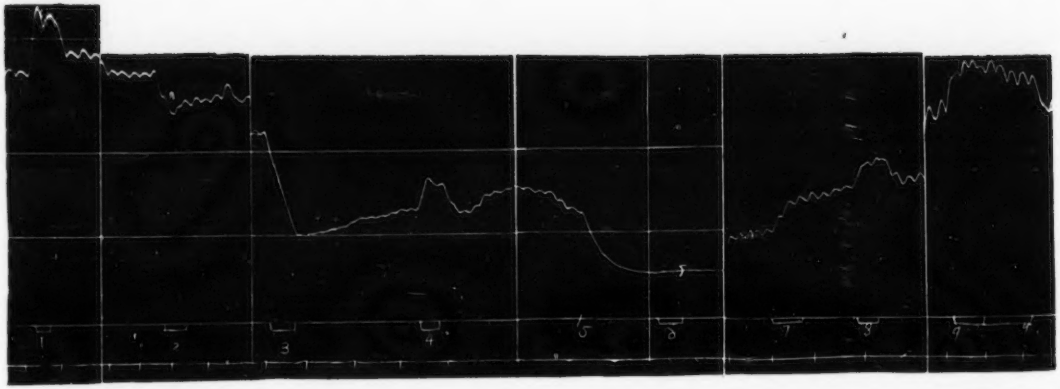

Fig. I. Effect of successive hemorrhages on the blood pressure, perfusion flow and sciatic stimulation, and the reinjection of the defibrinated blood. Experiment 27. Dog, spleen perfused, vagotomy; curare and oxygen insufflation. Upper curve = blood pressure from mercury manometer. Signal line = zero blood pressure. Lower line = outflow in units. (One-half natural size).

1, Sciatic stimulation; *2*, hemorrhage of 10 cc. per kgm. (total 20 cc. per kgm.)—note the decrease in flow; *3*, hemorrhage of 10 cc. per kgm. (total 40 cc. per kgm.)—note the further decrease in flow; *4*, sciatic stimulation; *5*, hemorrhage—10 cc. per kgn. (total 50 cc. per kgm); *6*, sciatic stimulation—no effect on blood pressure; *7*, began the reinjection of blood in divided quantities between *7* and *9*; *8*, sciatic stimulation; *9*, sciatic stimulation. (The tracing has been interrupted at various points)

tor centre is therefore successively stimulated, depressed and paralyzed.

If the blood is reinjected while the vessels are still constricting or dilating, i.e., before the paralysis has become complete, then the centre recovers its tone, and the blood pressure returns to normal. (With the injection of saline solution in one experiment, recovery was only temporary.) If, on the other hand, the dilation has become maximal before the hemorrhage is completed (i.e., when there is no further dilation toward the end of the hemorrhage), then the centre cannot be restored. The blood pressure in this case can only be brought to about 60 mm., no matter how much fluid is injected.

The rate of progress of these stages varies somewhat in different animals; in the mean, the constriction proceeds until the hemorrhage has reached about 25 cc. per kilogram, or when the blood pressure has fallen to about 95 mm. At this point the dilation sets in, which proceeds until paralysis occurs—usually when the hemorrhage amounts to 37.5 cc. per kilogram, and the blood pressure has fallen to about 30 mm.

As an illustration of the typical result of repeated hemorrhages, namely, successive constriction, dilation and paralysis, experiment 48 will be described somewhat in detail. A hemorrhage of 10 cc. reduced the blood pressure from 145 to 130 mm., and decreased the perfusion flow by 15 per cent (from 4.3 to 3.6 units); further hemorrhages of 10 cc. each, or 50 cc. in all, produced a gradually increasing vasodilation (to 5 units), the outflow rising to 10 per cent above the original, and the blood pressure falling to 38 mm.; at this stage the center became paralyzed, not reacting to sciatic stimulation. Prompt injection of the defibrinated blood partially restored the blood pressure (62 mm.), but did not restore the vasomotor tone; the perfusion flow became slightly decreased, but did not return to normal.

Attention might be called to the convenience of this method (exsanguination and reinjection of blood) for obtaining complete paralysis of the vasomotor centre for experimental purposes. This also gives a means for ascertaining the tone of the vasomotor centre. In two of our experiments the flow with the centre paralyzed was only 110 per cent of that with the centre intact;

in another, it was 220 per cent. But of course the exposure and handling of the splenic nerves and vessels may have lowered the vascular tone locally.

The period of vasoconstriction. Central vasoconstriction was observed in five experiments (C. 25, 27, 48, 49, 50). The centre was stimulated when the hemorrhage was comparatively small, usually with 5 to 10 cc. per kilogram; the stimulation persisted until a mean loss of blood of about 25 cc. per kilogram, extremes of 5 cc. (C. 25) and 40 cc. (C. 27). The period of constriction merged into the period of dilation when the mean blood pressure was 90 to 100 mm., extremes of 68 mm. (C. 27) and 150 mm. (C. 50). The mean decrease in perfusion flow was about 30 per cent, extremes of 8 per cent (C. 25) and 40 per cent (C. 50).

Cause of the vasoconstrictor stimulation. The stimulation of the vasomotor centre by hemorrhage is probably due to anemia of the centre from the decreased blood supply. Asphyxia was excluded, as all animals but one were curarized and received oxygen insufflation, which of course was not interrupted during the hemorrhage. The effects of asphyxia, as described in a previous paper,[3] are in the same direction, that is, stimulation of the centre, but of far greater degree. Central vasomotor stimulation results from other conditions of low blood pressure, i.e., that caused by nitrites, vagus stimulation, etc., and hence is not peculiar to the low blood pressure from loss of blood. The stimulation of the centre by hemorrhage has been shown in another manner by Cope.[4] He found the peripheral resistance in the arterial system usually increased during hemorrhage from the carotid artery; when the resistance decreased (probably from central vasomotor depression as indicated in our work), the blood pressure did not recover as well.

The period of vasodilation. This followed the vasoconstriction in five experiments (C. 18, 25, 27, 48, 50), when a mean of about 25 cc. of blood had been withdrawn, extremes 5 cc. (C. 18) and 50 cc. (C. 27 and 48). The perfusion flow in this period was much increased; on a basis of the normal as 100 per cent, the

[3] Sollmann and Pilcher: This Journal, 1911, xxix: 100.

[4] Cope, Otis M.: This Journal, 1911–12, 29: 137.

outflows were as follows: 60, 90, 110, 110, 220 per cent; the flow therefore returned to about normal or greater in all but one experiment (50). In the experiments showing an outflow (60 per cent and 90 per cent) below the normal, the outflow was increased over that of the period of constriction.

The 220 per cent dilation which occurred in experiment 18, was not preceded by constriction, but the conditions were anomalous. Previous to the hemorrhage, normal saline infusion had resulted in an abnormal rise in blood pressure (from 78 to 100), which was well sustained; during this maintained rise, the perfusion flow was greatly lessened, so that it seems to follow that the primary vasodilation in this experiment was really due to a relief of the previous abnormal vasoconstriction. (The experiment will be discussed further under saline infusion.)

Vasomotor paralysis. When the vasodilation had reached its maximum, vasomotor paralysis set in, so that the centre did not react to sciatic stimulation, and the outflow remained practically unchanged. The typical course of the experiment was interrupted at times by the injection of saline solution or defibrinated blood, a procedure to be discussed next.

Restoration of the anemic centre by prompt reinjection of defibrinated blood. This is successful, provided that the anemic paralysis has not gone too far. As the blood pressure returns to normal, the paralytic vasodilation is also relieved and the vessels constrict to the normal flow (expt. 27). If the vasodilation has not set in, the reinjection of the blood does not constrict the vessels (expt. C. 49).

Experiment C. 27. Successive hemorrhages of a total of 50 cc. had reduced the blood pressure from 150 to 28 mm., and the outflow from 4.3 to 2.8 units. At this level the outflow was beginning to increase (3.7 units) and sciatic stimulation was negative, so that the period of vasodilation was setting in. Reinjection of 40 cc. of blood resulted in a return of blood pressure nearly to the normal (130 mm.), and the outflow to a little above the normal (4.7 units). The blood pressure rose 30 mm. on sciatic stimulation, nearly attaining the normal rise (40 mm.) before the hemorrhage (fig. I).

Experiment 49. The hemorrhage (35 cc. per kilogram) had reduced the blood pressure from 115 to 42, with considerable reduction in out-

flow. Prompt reinjection of blood caused a return of pressure to 100 mm.; the outflow, however, did not increase. A constrictor response was obtained later by asphyxia.

Restoration of the anemic centre by infusion of saline solution. This also may be effective.

Experiment 25. A hemorrhage of 30 cc. per kilogram had resulted in successive vasoconstriction and dilation and loss of sciatic reaction as the pressure fell from 170 to 30 mm.; infusion of saline, 25 cc. per kilogram, restored the blood pressure temporarily to 90 mm., caused considerable decrease in outflow (5 to 3.2 units) and restoration of the sciatic reaction, so that sciatic stimulation gave a rise in pressure of 20 mm. (80 to 100 mm.). Reinjection of blood restored the blood pressure to 124 mm., with very little change in outflow; the sciatic reaction was not tested. The experiment was terminated shortly after by coal gas asphyxia.

Failure of recovery from complete paralysis. If the vasodilation following the hemorrhage has become maximal and sciatic stimu- negative, infusion of saline or blood or both does not restore the vasomotor tone, nor cause the blood pressure to approach the normal.

This phenomenon is illustrated in three experiments (C. 18, 48, 50):

Hemorrhage had reduced the blood pressure to 40, 38 and 30 mm.; the sciatic reaction was negative; the outflow after a primary decrease had increased above the normal in experiments C. 18 and 48, and although the dilation was very slight in experiment C. 50, it gave no further increase; reinjection of blood restored the blood pressure to 70, 60 and 80 mm.; the sciatic reaction was not restored and the perfusion flow was practically unchanged. In experiment C. 18, saline infusion (40 cc. per kilogram) before the blood infusion, raised the blood pressure from 40 to 60 mm., but had no other effect. Saline infusions following the blood infusion (10 cc. per kilogram) increased the pressure from 80 to 110 temporarily, and there was a slight restoration of the sciatic reaction, which, however, soon failed.

Our experiments do not permit us to decide whether this altered pressure-response after slight hemorrhage is due to changes in

the vasomotor centre, in the vascular tone, or in the distribution of the blood.

Sciatic stimulation after hemorrhage. The experiments show that the blood pressure response is decreased during the anemic stimulation, and still more during the anemic depression of the centre. Even small hemorrhages (5 to 10 cc.) lessen the pressure-response to sciatic stimulation very greatly, although the level of blood pressure may have been but slightly lowered. As increasing quantities of blood are withdrawn, the reaction becomes less and less, and ceases entirely when a somewhat variable low blood pressure is reached. The reaction was lessened in each of seven stimulations when the level of pressure was above 100 mm., and once at 90 mm. To cite one experiment (C. 50): following a hemorrhage of 5 cc. per kilogram, the rise was diminished from 58 to 30 mm., while the level of blood pressure was practically unchanged (150 mm.). A further withdrawal of 10 cc. per kilogram reduced the level to 130 mm. and lessened the sciatic reaction to 20 mm.

The perfusion flow reaction to sciatic stimulation after hemorrhage was somewhat variable. Usually, however, the constrictor response seemed to be somewhat greater after the loss of small quantities of blood, and the reaction failed somewhat earlier than the blood pressure response (C. 48, 50, 27). The outflow variations seem scarcely great enough to warrant further analysis.

The numerical data are shown in table I. They differ somewhat from those recorded by Porter and Marks.[5]

In each experiment, the upper numbers show the level of blood pressure; the second line, the rise of pressure on sciatic stimulation; the third line, the change in blood flow in units (slowing signifies central vasoconstriction).

Loss of but 5 cc. of blood in two experiments (C. 37, 50) lessened the absolute and percentile rise in blood pressure by one-half. In the third experiment (C. 48), a 10 cc. hemorrhage lessened the response to one-fourth the original. In each case the residual pressure was above 130 mm. (160, 130, 142). The next hemorrhage of 10 cc. did not mate-

[5] Porter and Marks: This Journal, 1908, xxi: 460.

rially alter the absolute rise in blood pressure but the percentile rise was somewhat increased. The reaction disappeared when 35, 40 and 40 cc. of blood were lost with the blood pressure at 38, 45 and 60 mm.

In other experiments the sciatic reaction was not tested regularly, but a positive reaction persisted until a low level of pressure was reached (C. 8, 30, 58). In experiment C. 27, the sciatic was stimulated only after 40 cc. had been withdrawn; the rise in pressure was quite unusual, from 57 to 86 mm. (29 mm.), almost as great as before any hemorrhage (150 to 190 mm.).

TABLE I

Blood pressure and outflow response to sciatic stimulation after hemorrhage

EXPERIMENT	HEMORRHAGE CC. PER KG.									
	0	5	10	15	20	25	30	35	40	50
37	175			100			67		38	
	35			16			9		0	
	4-3.6			5.2-5			3.5-3.2			
48	140		130		118		108		60	50
	25		8		6		10		0	0
	3.4-3.3		3-2.8		2.8-3		3.2-3.2		3.8-3.8	
50	150	150		130		90		45		
	58	30		20		10		0		
	4-3.6	4.2-3.7		3.2-2.7		2.5-2.5		2.9-2.9		
18	100				118		58		40	
	16				6		0		0	
	3.0-2.6				3.-3.		3.-3.		3.-3.	

In the five experiments in which the sciatic reaction was tested, the mean level of blood pressure at which the vasomotor center became paralyzed lay about 35 to 40 mm. (28, 30, 30, 38, 58, 60 mm.). The level was probably somewhat higher, as the mean level, before the final hemorrhage that abolished the reaction, was considerably higher.

The low blood pressure ("shock") level depends chiefly on the amount of blood lost and not to an important degree on the rapidity of the hemorrhage. It might be expected that the total quantity of blood that could be withdrawn, before the low blood pressure level was reached, would depend in part at least on the rate of withdrawal; that the organism would adapt itself to a gradual hemorrhage more readily than to a sudden hemorrhage. This

was not the usual course of events in these experiments. In table II the experiments are arranged according to the time which elapsed before the low level of blood pressure was reached.

A glance at the table will show that the quantity of blood withdrawn, although variable, determines the final low blood pressure ("shock") level; and that the rate of withdrawal is relatively unimportant. For instance, in experiment C. 27, 40 cc. was withdrawn in $4\frac{1}{2}$ minutes, but the pressure fell only to a moderate level. A further hemorrhage of 10 cc. lowered it to shock-level. In experiments C. 25, 18 and 37, the low pressure of 30 to 40 mm. was reached after withdrawing 40 cc. of blood, in periods ranging from $4\frac{1}{2}$ to 25 minutes.

TABLE II

The original blood pressure; total amount of hemorrhage in cc. per kilogram, time between first and last hemorrhage and the final level of blood after the final hemorrhage

EXPERIMENT	ORIGINAL BLOOD PRESSURE	TOTAL HEMORRHAGE	TIME BETWEEN FIRST AND LAST HEMORRHAGE	FINAL LEVEL OF BLOOD PRESSURE
25	170	20	4.5	30
27	150	40	4.5	68
		50	11	28
18	120	40	12	40
48	145	50	13	38
49	115	30	16	49
50	148	30	19	30
37	183	40	25	38

The mean quantity of blood lost in the seven experiments was 35 cc. per kilogram; the extremes 20 and 50 cc. During the experimentation no effort was made to bleed the animal at uniform rates either for the fractional or total hemorrhage.

Fall in blood pressure with successive hemorrhages. The relation of the fall of pressure to the amount of blood lost, varies in each animal, as shown in figure II. However, the median type, shown by the heavy curve, is approached more or less closely by most of the experiments. It shows that the rate of fall, per each 5 cc. loss of blood per kilogram, increases gradually with the total amount of blood lost. The percentile fall, of course,

increases still more. It is also worth noting that the animals with relatively low initial blood pressure showed a relatively slow fall in the hemorrhage; whilst the most rapid falls occurred in the animals with the highest initial pressure.

Dawson[6] concluded that the fall in pressure from hemorrhage does not depend closely upon the amount of blood withdrawn,

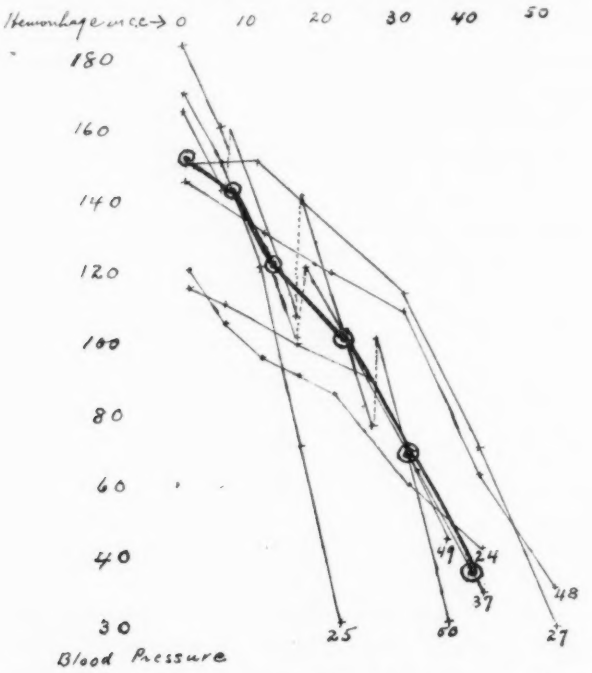

FIG. II. Fall in blood pressure in millimeters with successive hemorrhages; hemorrhage in cubic centimeters per kilogram of body weight. Dotted line indicates the recovery in blood pressure between hemorrhages. Heavy line indicates the median blood pressure in all experiments.

and attributes it to the fact that the quantity of blood varies in different animals; the cardiac weakening from the loss of blood is a variable factor; the amount of peripheral constriction due

[6] P. M. Dawson: Jour. Exp. Med., 1905, vii: 1.

to anemia might vary in different animals. The latter postulate so far as the central influence on the peripheral vessels is concerned, is established by the results given in this paper.

The effect of previous saline infusion on the phenomena of hemorrhage. Our data are not sufficient to permit generalizations. Two of the three dogs that received normal saline reacted abnormally to it. In experiments C. 18 and 48, infusion of saline (36 and 95 cc. per kilogram) caused a rise in blood pressure from 70 to 100, and 103 to 112, with unusually great vasoconstriction (20 and 47 per cent). In each case hemorrhage resulted in relief of the vasoconstriction, immediately in 18 and after loss of 10 cc. of blood in 48.[7] The third animal (C. 27) reacted in the usual manner both to the saline infusion and to the succeeding hemorrhage.

CONCLUSIONS

1. Hemorrhage progressively stimulates, depresses and paralyzes the vasomotor centre.

2. The period of stimulation is somewhat variable, but usually persists during a total hemorrhage of about 25 cc. per kilogram when the blood pressure has fallen to about 90 to 100 mm.

3. A period of vasodilation follows the stimulation; the perfusion flow may remain below the normal, return to the normal, or increase somewhat above the normal flow.

4. The centre becomes paralyzed when about 35 to 40 cc. per kilogram has been withdrawn and when the blood pressure has reached a low level (approximately 30 mm.).

5. Reinjection of blood or saline solution before the onset of paralysis may restore the vasomotor tone.

6. The low blood pressure (shock) level depends chiefly on the amount of blood lost and not to an important degree on the rapidity of the hemorrhage.

7. The relation of the fall of blood pressure to the amount of blood lost varies in each animal; however the median type is approached more or less closely by each experiment.

[7] Experiments are to be described further under the "Effect of Saline Infusion" in the next paper.

STUDIES ON THE VASOMOTOR CENTRE: THE EFFECTS OF INTRAVENOUS INFUSION OF NORMAL SALINE SOLUTION

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INTRODUCTION

The increase of organ volume which ordinarily follows saline injections, could be interpreted as a sign of central vasodilation. This need not necessarily follow; vasodilation could be peripheral or cardiac or purely mechanical. In fact, the following experiments made with our usual technique[1] shows that intravenous saline injections (0.9 per cent NaCl at room temperature) ranging from 1 to 90 cc. per kilogram tend to stimulate the vasomotor centre. Often, however, they do not affect it at all.

Behavior of the vasomotor centre when the saline injection leaves the blood pressure nearly unchanged. In normal animals, saline injections from 10 to 45 cc. per kilogram generally leave the blood pressure unchanged or produce only a slight and short rise. Under these conditions, the vasomotor response displays either an inconsiderable constriction or no response at all. This was the case 7 times in 10 experiments (10 animals).

In three of these experiments (C.92, cat, 71, 109) there was constriction of slight degree (2, 6, 12 per cent), while the pressure remained normal; in four of the experiments (C.27, 55, 48, 94) the outflow remained constant, and the pressure rose or fell very slightly. There was one kidney perfused in each of these groups, so that the kidney probably reacts as the spleen to intravenous saline infusion.

[1] Sollmann and Pilcher: This Journal, 1910, vol. xxvi: 233.

Results when the rise of blood pressure is more prolonged. This occurred in three experiments, with injections of 10 to 90 cc. per kilogram. All showed more pronounced constriction—10 to 50 per cent. This may partly explain the more prolonged rise. Constriction is also indicated by the relation to the diastolic and systolic blood pressure. The Huerthle membrane manometer indicates vasoconstriction, i.e., an elevation of the diastolic level of blood pressure greater than the increase in systolic level: the diastolic level was raised in experiments C. 18 and 48, and temporarily very slightly lowered in C. 37, not sufficiently to hold against vasoconstriction. If the increased blood pressure depended on the increase in circulating fluid, the excursion would be increased fairly equally in the systolic and diastolic directions. Of course the increased volume of fluid contributes to the rise.

Cause of the differences in the vasomotor and blood pressure response. Two of the animals (37 and 18) which showed the more sustained and powerful vasoconstriction were curarized, with oxygen supplied by insufflation. Both had an asphyxial tendency, and therefore presumably a heightened vasomotor irritability, which is the probable explanation of the exaggerated vasomotor response. This was shown directly in experiment 37 by unusually powerful constriction from sciatic stimulation. The quantity of saline in both cases was moderate (5 to 25 cc. per kg.). In the third experiment (48), no curare was given, and the animal breathed naturally. In this case, an unusually large amount of saline (90 cc.) was injected, which may account for the exaggerated effect.

The level of blood pressure on vasomotor response. The vasomotor response to saline infusion was not influenced by the level of blood pressure between 60 and 170 mm. (see table I). However, if the saline infusion be given after hemorrhage has reduced the pressure to a very low level and partially or completely abolished vasomotor response to saline infusion, the tone of the centre may be restored.[2]

[2] Paper on Hemorrhage of this series: This Journal.

Transfusion of blood into a normal dog. This was observed in but one animal (C. 11). The blood was transfused into the femoral vein for about two minutes; the quantity received was not measured; there was a fairly prompt rise in blood pressure from 110 to 138 mm., with an increase in perfusion flow from 3 to 4 units. The pressure and dilation were maintained about seven minutes, when both returned to the original level rather promptly. This result is in striking contrast with those of saline infusion, the saline causing constriction, the transfusion dilation. We have not investigated whether the difference is uniform, or whether this animal happened to be exceptional.

TABLE I

Level of blood pressure on vasomotor response to saline infusion

BLOOD PRESSURE	60-100	100-140	140-170
Constriction	2	2	4 *
Negative	2	2	1

Figures represent the number of experiments at each level.

* Three infusions into one dog (37).

CONCLUSIONS

1. In normal animals the intravenous infusion of saline solution (10 to 40 cc. per kg.) slightly stimulates the vasomotor centre or leaves it unchanged.

2. Occasionally, when the saline causes a maintained rise in blood pressure, there may be considerable stimulation of the centre. This variation is probably due to a hypersensitive centre.

3. Above a 60 mm. level, the original blood pressure seems to have no influence on the response of the vasomotor centre.

OBSERVATIONS ON THE VENOUS BLOOD PRESSURE IN MAN

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INTRODUCTION

In an earlier paper[1] the effect of muscular exercise, particularly in man, upon the venous blood pressure, was reported. It is proposed here to deal with the diurnal variations in venous pressure, and to report certain other observations upon the influence of experimental conditions as modifying that pressure.

The efforts of Frey,[2] v. Basch,[3] Gaertner,[4] Sewall,[5] and Oliver,[6] to study venous pressure in man, unfortunately stimulated little interest in the subject. In 1906, v. Recklinghausen,[7] published the description of a method by which he was enabled to obtain accurate determinations. With a modification of v. Recklinghausen's instrument, Hooker and Eyster[8] investigated a few clinical cases and sought, in two normal individuals for evidence of diurnal variations in the venous pressure. Although their results were inconclusive as to a diurnal variation they evidenced considerable variation in the venous pressure during the periods of observation. No parallelism was noted between the venous pressure and either the pulse rate or the arterial pressure. The

[1] Hooker: American Journal of Physiology, 1911, xxviii, 235.

[2] Frey: Deutsches Archiv für Klinische Medicin, 1902, lxxiii, 511.

[3] v. Basch: Wiener Medicinische Presse, 1904, 962.

[4] Gaetner: Münchner Medicinische Wochenschrift, 1904, lxxiv, 2038.

[5] Sewall: Journal American Medical Association, 1906, xlvii, 1279.

[6] Oliver: Journal of Physiology, 1898, xxiii, v.

[7] v. Recklinghausen: Archiv für Experimentelle Pathologie und Pharmacologie, 1906, lv, 463.

[8] Hooker and Eyster: Johns Hopkins Hospital Bulletin, 1908, xix, 274.

values for the normal venous pressure obtained by v. Recklinghausen and Eyster and Hooker agree fairly well with the results of measurement by means of a hollow needle introduced directly into the vein as reported by Moritz and v. Tabora,[9] Schott,[10] and others.

A further modification of the instrumental method introduced by v. Recklinghausen has been used in the present experiments. v. Recklinghausen used a circular bag of thin rubber, about 5.5 cm. in diameter, with a small opening above and below. The lower surface was made air-tight against the skin, with a coating of glycerine, the upper opening being closed by a glass plate held in the hand. Into this bag air was then forced until the superficial vein as seen through the glass was collapsed, and the pressure required was read on a connecting water manometer. Eyster and Hooker used in place of the rubber bag a small glass-topped box with a rubber bottom, through an opening in which the vein could be observed. The box was held in position by means of binding tapes. The air pressure was regulated by screw compression of a rubber bulb.

DESCRIPTION OF APPARATUS

The instrument in its present form is shown in figure 1. It consists of a small cup (*A*) 20 mm. in diameter, and 10 mm. high, made of glass about 1 mm. thick. At the side a glass tube slightly tapered serves to connect the chamber with the water manometer. On the back of the manometer is a small camera bulb (*B*) about 30 mm. long which by a T-opening connects with the manometer and the tube leading to the glass chamber. An oval plate is brought to bear upon the bulb by compression with the fingers, thus producing the pressure required to collapse the vein under observation. A rachet (*C*) held against the plate by a spiral spring maintains any degree of compression of the bulb, release of which is accomplished by a slight rolling movement of the finger. The bore of the manometer is 3.5 mm., so that

[9] Moritz and v. Tabora: Deutsches Archiv für Klinische Medizin, lxxxviii.
[10] Schott: Deutsches Archiv für Klinische Medizin, 1912, cviii, 537.

when one end is closed by a catch, the water will not run out, even when the instrument is inverted. The legs of the manometer-stand fold up, and the instrument slips into a case 330 x 40 mm. For convenience a hand rest (*D*) is provided. A brass rod graduated in centimeters is held by a neck piece vertically in front of the thorax. On this rod a hand rest may be adjusted so that the observed vein is subject to a suitable hydrostatic

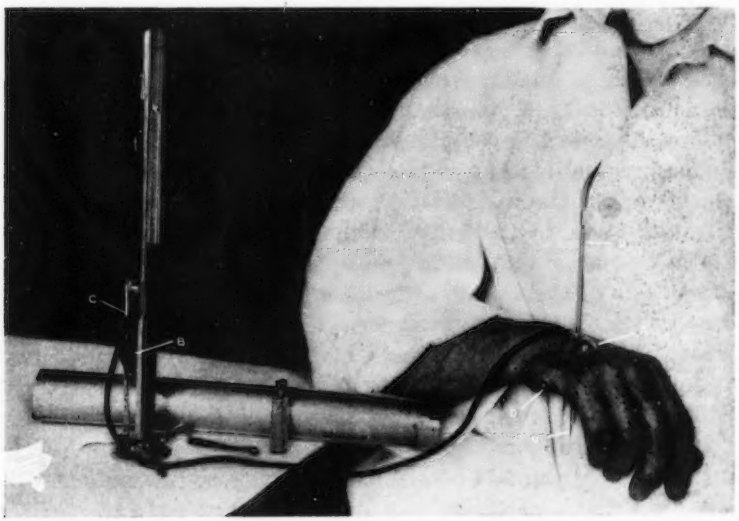

Fig. 1.

pressure which may be known by reading the number of centimeter divisions on the rod between the vein and the chosen heart level.

USE OF THE INSTRUMENT

The essential part of the apparatus thus described is the glass chamber. It is applied over a vein in the following manner. With the hand of the subject on the rest and illuminated so that the vein selected gives a distinct shadow, the chamber is laid in position and held with a small rubber band circling the hand.

A film of collodion is placed in the angle formed with the skin. When this is dry the rubber band is removed, The effect of the collodion, aside from sealing the chamber to the skin, is to draw the surrounding tissues so that the encircled area is free from tension. When air is now forced into the chamber, the latter is raised slightly, but the contour of the skin over the vein is not disturbed until the pressure equals the venous pressure at which point the vein shadow disappears. Some nicety of judgment is often required to establish this point. Experience has shown that the most consistent results are obtained when the reading is made at the point where slight oscillations of pressure cause the vein shadow to come and go promptly just before the vessel is completely collapsed.

The pressure reading thus obtained gives the venous pressure plus or minus the hydrostatic column extending from the point of observation to the heart level. v. Recklinghausen selected the mid-point of the anterio-posterior diameter of the body at the bottom of the sternum (costal angle) for the heart level, and the same point has been used in present observations. Any convenient point, however arbitrary, serves its purpose for comparative determinations on the same individual maintaining the same (erect) body position. At present no data are at hand to establish accurately the relationship of this point to the right auricle. Age, sex and bodily position may show differences in this relationship, sufficient to introduce serious error. On the other hand, differences in the pressure values observed under these conditions may represent true differences in the venous pressure. Determinations of venous pressure in students indicate that when the pressures are referred to the above level, there is a markedly lower pressure in woman than in man. In general, however, vigorous individuals have more conspicuous superficial veins, a fact which may be interpreted to mean a relatively higher pressure than is present in those of a more sedentary habit. This might account for the lower pressures observed in women.

Roentgen examination has made clear that the heart is more readily movable than was formerly supposed, and that altered

conditions disturbing the position of the diaphragm alter correspondingly the position of the heart. According to Dietlen[11] the upper border of the heart in women and children lies behind the second interspace while in men it lies behind the third rib. The lower border (right auricle) would presumably show the same slight difference. Dietlen also states that in assuming the vertical body position, the heart (upper border) descends 2 to 4.5 cm., and that in old age the heart lies at a lower level—the upper border being behind the third rib in the second decade and behind the third interspace in the seventh decade. Unfortunately, none of these measurements bears directly upon the relationship of the right auricle to the sub-costal angle. It is possible that variations in the shape of the thorax would show still further differences. The figures published by Dietlen indicate that the right auricle is farther above the sub-costal angle in women than in men, a factor which, as a source of error, should yield higher pressures for women than men, which is contrary to observations thus far made. The change in the position of the heart when assuming the upright from the recumbent position is of more significance. This should result in higher readings when the trunk is vertical, than when horizontal, which accords with few observations made and will be discussed on another page.

Animal experiments have, in general, lent support to the belief that venous pressure rises and falls inversely to the arterial pressure.[12] That the venous system is supplied with motor nerves is, however, now well established. The observations of Mall[13] on the portal vein, of Roy and Sherrington[14] on the veins of the neck, and of Thompson[15] and Bancroft[16] on the veins of the leg, are decisive, especially in view of the evidence presented by Gunn and Chavasse[17] that the veins respond to epinephrin with

[11] Dietlen: Ergebnisse der Physiologie, 1910, x, 598.
[12] Plumier: Archives internationales de Physiologie, 1909, viii, I.
[13] Mall: Archive für Physiologie, 1892, 409.
[14] Roy and Sherrington: Journal of Physiology, 1890, xi, 85.
[15] Thompson: Archive für Physiologie, 1893, 102.
[16] Bancroft: American Journal of Physiology; 1898, i, 477.
[17] Gunn and Chavasse: Proceedings Royal Society, 1913, series B, lxxxvi, 192.

constriction, a reaction which is now accepted as proof of sympathetic innervation. Although the evidence available at the present time is insufficient to establish definitely the existence of a veno-motor system comparable to the vaso-motor system proper, none of the evidence is against such an hypothetical nervous mechanism, and much of the data is impossible of explanation without such an assumption. It remains a fact, however, that no direct experimental proof has as yet been put forth.

OBSERVATIONS

1. Diurnal variations in venous pressure. This series comprises fifteen observations on the author, single observations on three surgical cases confined to bed in the hospital, and three observations on an individual during the sleeping period, two of which were made during the day at a time when he was working at night, and one during the night when he was working in the day time. In addition the forenoon and afternoon observations on twenty-three students made by their coworkers are also given. The series demonstrates conclusively that the venous pressure tends to rise progressively during the waking hours, and to fall in the same way during the sleeping hours.

It has been accepted from short lasting experiments on animals that the venous pressure passively rises and falls with changes in the peripheral resistance. When, however, the results here reported are compared with observations on the diurnal rhythm in the arterial pressures, no such relationship is found to exist. The observation of Tarchanoff[18] that the arterial pressure of young dogs falls in sleep and rises when they are awake, has been abundantly confirmed on man. Brush and Fayerweather,[19] and Brooks and Carroll[20] have shown that the arterial pressures in man are distinctly lower at night (in sleep) than in day time. Erlanger and Hooker[21] in a series of carefully controlled observations on man, found a tendency for both the

[18] Tarchanoff: Archives italiennes de Biologie, 1894, xxi, 318.
[19] Brush and Fayerweather: American Journal of Physiology, 1901, v, 199.
[20] Brooks and Carroll: Archives of Internal Medicine, 1912, x, 97.
[21] Erlanger and Hooker: Johns Hopkins Hospital Reports, 1904, xii.

systolic and diastolic arterial pressures to rise throughout the day. This rise in pressure was more clearly marked in the case of the pulse pressure, the rise of which, in conjunction with an increased pulse rate, was interpreted to indicate an increased velocity of blood flow in the aorta. If the diastolic pressure be interpreted to indicate peripheral resistance or the degree of vaso-constriction, there is no evidence that under normal conditions of life the peripheral resistance alone controls the magnitude of the venous pressure. The results reported in this paper suggest rather that the pressure in the venous system is dominated by a special nervous mechanism. This is in accordance with Henderson's[22] hypothesis for the volume output of the heart, and with some unpublished results of Morison in this laboratory on the relationship of venous pressure to the condition of surgical shock.

Of the fifteen observations upon the author made by himself, five are presented as plotted curves in figure 2. Of these the experiments of January 2 and 3 were performed upon days of usual laboratory routine, the experiments of January 4 and 11 on days of unusual quiet (Sundays). The experiment of January 5 was performed upon a day in which the morning was very quiet and the afternoon devoted to a long fatiguing (10 mile) walk. The procedures noted in connection with the curves are sufficient explanation of the experimental conditions. It will be noted that the pressure is close to 10 cm. of water in the morning before getting out of bed. It then rises, usually irregularly, throughout the forenoon. After midday there is a tendency for the pressure to drop somewhat, after which a rather continuous rise follows, lasting until bedtime, when it is in the neighborhood of 20 cm.

In connection with one of these experiments, the pulse rate was recorded, but showed absolutely no relationship to the changes in venous pressure. The three surgical cases confined to bed in the hospital showed the same general rise of venous pressure. As in the examples above quoted, these individuals (men) showed decided fluctuations in the pressure, although not to the same

[22] Henderson and Barringer: American Journal of Physiology, 1913, xxxi, 352.

degree. During the observations, extending from 10 a.m. until 6.30 p.m., they were lying quietly in bed. The lowest and highest readings were respectively 5 and 15, 5 and 15, and 3 and 15 cm. These subjects were 30 years, 38 years, and 20 years old respectively.

In comparison with the pressure values in the hospital cases who were physically quite inactive, the approximate averages for

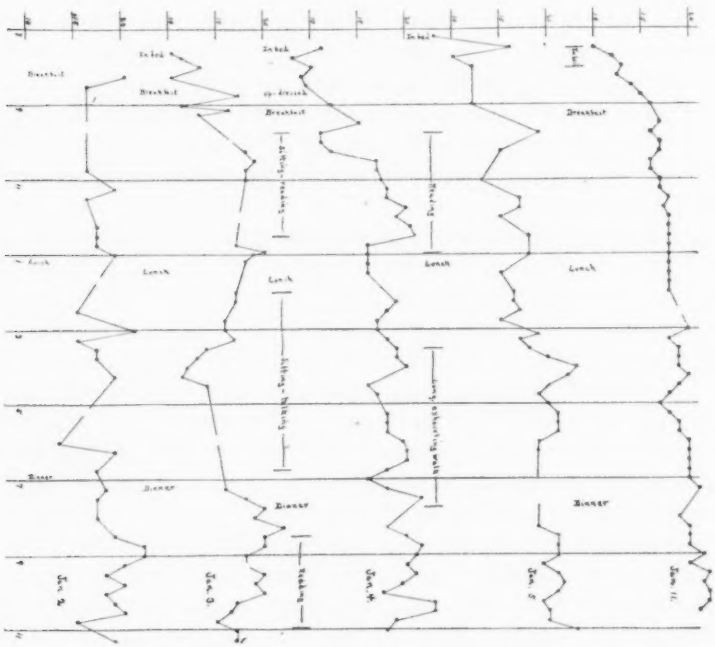

Fig. 2. Curves of diurnal variation in venous pressure.

morning, noon and evening observations on the author show distinctly higher values which may be ascribed to a greater amount of physical exertion. These are, for the early forenoon 12, for midday 18, and for evening 20 cm.

All the observations upon the author were made with the trunk in the vertical position. The effect of this position, in compari-

son with the trunk-horizontal position, may be to drop the right auricle with respect to the subcostal angle. We should expect, therefore, to obtain lower values for the venous pressure in the upright position. The lower readings for the hospital cases might again be explained on the assumption that the mid-point of the auterior-posterior diameter of the body at the subcostal angle is above the auricle level in the recumbent posture. No data are, however, available on this point, hence the conclusion that the lower values in the three hospital subjects are due to lesser amount of muscular activity. The observations on the sleeping individual, now to be considered, will raise this point for further consideration.

The results thus far presented evidence the progressive rise in venous pressure during the waking hours. It remains to discuss the results obtained from observations during sleep. The subject of these observations was a young man of 22 years, who was on two-week periods of night work, alternating with two-week periods of day work. The results of the three observations made are plotted in figure 3. The incidental notes are here presented.

Experiment of February 3. The subject had been at work from 11.00 p.m. until 8.00 a.m. The first reading was made at 9.40 a.m. after he had been seated quietly for five minutes. He then bathed and lay down to sleep at 10.10 a.m. Although asleep at 10.45 a.m. he was restless and awake the greater part of the forenoon. From 1.00 p.m. until 2.30 p.m. he was sound asleep and was not disturbed by the observations. At 3.00 p.m. he was restless again. At 3 30 p.m. he was awake, and at 4.00 p.m. he was wide awake and ready to get up. He complained that he had not rested well, and did not feel refreshed, a usual experience when he had to take his sleep in the day time. For a half-hour after 5.00 p.m. he took vigorous exercise out of doors.

At 10.45 a.m. and thereafter until 3.30 p.m. there was noted a remarkable pulsation in the vein of the hand under observation. This pulse was peripheral in origin, and when the vein was submitted to proper compression there spread under the compressed area, with each arterial pulse, a distinctly visible wave. Occlusion of the vein centrally was without effect, but peripheral occlusion caused the pulsation to disappear. The same pulsation in the vein was noted in the two other

observations during sleep, but it was never seen with convincing clearness on any of the subjects during the waking period of the day. This pulsation of the vein lends very strong additional support to the experimental observation that the peripheral arteries of the skin are dilated in sleep.[23]

One other incidental observation in this experiment is worthy of note. At 4.20 p.m., soon after the subject was up, the vein had a diameter of 4 to 5 mm., at 4.40 p.m. the apparent diameter was reduced to 1 to 2

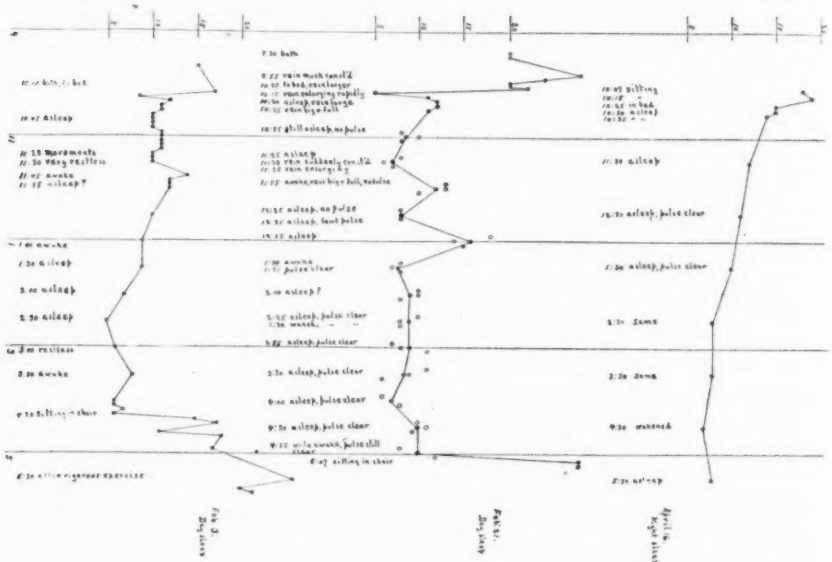

Fig. 3. Curves of diurnal variation in venous pressure. Venous pressure during sleep.

mm. Although the intervening reading had given a fall in the pressure of 7 cm., the pressure before and after the constriction was the same, i.e., 18 cm. This single chance observation of change in vein volume suggests that the veno-pressor mechanism, assuming one to exist, functions to maintain an optimum feeding pressure to the heart, an hypothesis put forward by Henderson. It is conceivable that the peripheral venous system collaborates with the portal system to this end, much

[23] Howell: Journal of Experimental Medicine, 1897, ii, 313.

as the peripheral arterial system collaborates with that of the splanchnic area in maintaining an equitable arterial pressure, so that both the pressure-flow and volume-flow to the heart balance with the physiological needs of the body under varying conditions.

Experiment of February 21. The conditions of this experiment were essentially the same as in the one just reported. The subject, however, rested better. The pulse in the vein was again visible. As noted on the plotted curve, the vein showed distinct variations in size. The pressure fell less after recumbent posture was assumed, but the fall at the time of lying down was much more marked than in the first experiment. The curve shows a similar marked rise in pressure when the subject assumed the upright position toward the end of the experiment. It is quite improbable that error in determining the heart level could explain this considerable pressure difference. It is natural therefore to conclude that the venous pressure is lower in the recumbent that in the upright position. In the last experiment the pressure fell only 4 cm., a relatively small decrease. As this experiment progressed, the pressure fell far more, however, and reached a correspondingly low value, i.e., 8 cm. Barach and Marks[24] in twenty-six normal individuals noted a similar change in venous pressure; in the erect posture their values varied between 8 and 18 cm., and in recumbent between 3.5 and 11 cm. These authors state that the venous pressure appears to vary in the same sense as the pulse pressure, and as this value is usually decreased on assuming the erect position, owing to the rise in diastolic pressure, it follows again that the venous pressure is not passively dependent upon the state of the arterial tone.

Experiment of April 16. In this experiment the subject took his rest at night. He slept much more soundly and continuously. He was awakened at 4.30 a.m. to ask at what time he wished to get up. In the morning he was refreshed and felt that he had had a good night's rest. Pulse in the vein was again visible. No notes were made as to the size of the vein. Fewer observations were made than in the other experiments, but the results are much more decisive. There was a progressive fall in pressure amounting finally to 7 cm. of water. The subject rose at 5.30 a.m., and because of haste no further readings were taken. Attention has been called to the fact that in this experiment the pressure fell less than in the others, only 4 cm., on assuming the recumbent posture. In the course of the night, however, it fell

[24] Barach and Marks: Archives of Internal Medicine, 1913, xi, 485.

more, and ultimately reached a value of 8 cm., comparable to the values found in the other experiments.

The data from the twenty-three students further substantiate the above results. The observations were made by the students themselves. One observation was made in the forenoon and another in the afternoon of the same day. Of the twenty-three students thus examined two gave a lower venous pressure in the afternoon, a fall of 7 cm. and 1.6 cm. respectively; twenty-one gave a decidedly higher afternoon reading so that the averages for the whole group were 12.4 cm. in the forenoon and 15.6 cm. in the afternoon. The two exceptions to the rule which showed lower afternoon readings may in all likelihood be explained by the irregularity in the progressive rise already noted.

2. Effect of local vascular tone. In two experiments on the author the effect of changes in local arterial tone produced by warming and cooling the hand, upon the venous pressure was studied. As the results obtained were entirely negative, the experiments require but brief consideration. The condition of local arterial tone was assumed to vary with the temperature of the part which was recorded by a special flat-bulbed thermometer insulated against the skin on the back of the hand. The hand was then placed for periods of from fifteen to fifty minutes alternately over a warm radiator, and over a large block of ice. The curve of venous pressure, although it varied, showed no relationship to the temperature curve. In the periods of cold it was necessary to increase the hydrostatic column by lowering the hand in order to get satisfactory readings, but the change in vein volume thus allowed for, did not express itself as a change in venous pressure, a fact which lends support to the earlier statement to the effect that the degree of dilatation of the vein is not necessarily related to the internal pressure.

3. Effect of alternation of intrathoracic pressure. By breathing into a mask through which fresh air streamed under a positive or negative atmospheric pressure, the intrathoracic pressure was presumably altered by an amount approximately equal to the change in the pressure of the air breathed. Erlanger and Hooker

made use of this procedure to see if changes in the renal venous pressure affected the output of albumin in a case of orthostatic albuminuria. Two experiments on the author with a positive pressure of 5 cm. water in inspiration and 20 cm. in expiration produced a rise of venous pressure of 6 cm. and 7 cm. respectively. The rise occurred sharply, about 4 cm. in the first five minutes, and fell off to the normal value, about 17 cm., with equal promptitude, when normal respiratory conditions were again established. The experiments were continued thirty-five and sixty minutes. Two experiments were likewise performed upon the author in breathing against a reduced atmospheric pressure. In the first the air pressure was −18 cm. water in inspiration, and −11 cm. in expiration. The venous pressure fell 3 cm. in a period of twenty minutes. In the second, lasting sixty minutes, with air pressures of −20 cm. and −13 cm., the venous pressure fell quickly at first, from 18 cm. to 15 cm. in five minutes, and then more slowly until the end of the period when it was 11 cm., a fall of 7 cm. It then rose to 14 cm. in the first five minutes after breathing under normal conditions, and was normal again at the end of the second five minutes.

The results in this series of experiments indicate that the effect produced upon the venous pressure by breathing air under different atmospheric conditions is purely mechanical. The disturbance in the normal aspiratory action of the thorax cannot be wholly compensated, at least in a period of one hour, which should be long enough for a return to the normal if the mechanism were capable of such an adjustment.

4. The values for normal venous pressure. The values for the venous pressure reported in this paper are somewhat higher than those previously given. There is reason to believe that they are more accurate. The weight and pressure of application of the older instrument together with the poorer illumination of the vein obtained with it may be sufficient to account for the different results. At any rate it is interesting to note that the values for the venous pressure now obtained are in better agreement with values reported by Henderson as normal to the proper

filling of the heart in diastole than are the older ones. The instrument in its present form has the added advantage that it may be left in place for an indefinite period. In the course of the present observations it was left on the hand continuously for several days with little or no inconvenience. This may prove a distinct convenience in observations on cases in hospital and under other similar conditions.

SUMMARY AND CONCLUSION

1. A modified instrument is described for the determination of venous blood pressure in man.

2. The venous pressure exhibits a distinct diurnal rhythm, rising throughout the day from 10 cm. to 20 cm. and falling again during the night.

3. Alterations in intrathoracic pressure produce an effect upon the venous pressure which cannot be compensated. When the intrathoracic pressure approaches atmospheric pressure, the venous pressure rises, and vice versa.

4. The data here gathered indicate that the normal venous pressure varies very considerably, averaging in the day time, under normal conditions, about 15 cm. of water.

5. In sleep, at night, it may fall to 7 to 8 cm.

6. The pressure measured in the veins of the hand is not influenced by local changes in vascular tone or by changes in pulse-rate.

7. The capacity of a vein may vary without affecting the internal pressure.

8. In sleep the veins exhibit a pulse of peripheral origin.

9. Normal venous pressure is independent of changes in peripheral arterial resistance.

10. The suggestion that an hypothetical veno-motor mechanism may function to maintain a constant feeding pressure to the heart is supported.

THE OUTFLOW OF BLOOD FROM THE LIVER AS AFFECTED BY VARIATIONS IN THE CONDITION OF THE PORTAL VEIN AND HEPATIC ARTERY

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The liver is the only gland in the animal body receiving both venous and arterial blood. The former is supplied to it at very low pressure by the way of the capacious portal vein, the latter, at very high pressure by the strikingly narrow hepatic arteries. Except for the relatively small amount which is supplied to the walls by the blood vessels and biliary ducts, none of the blood of the hepatic arteries mixes with that of the portal veins until the branches of the two vessels turn into the hepatic lobules. At the point where the two streams unite, that is to say, at the intrahepatic capillaries, their pressure must equal, which means that in its course in the interlobular connective tissue, the branches of the hepatic artery must offer an enormous resistance to the blood flowing through them. This frictional resistance resides in the arterioles and since these are richly supplied with active vasomotor nerves, great variations in hepatic inflow become possible.[1] On the other hand, although the portal venules are capable of active constriction and dilatation only to a slight degree,[2] it is possible that their caliber is very readily influenced by changes in the closely adjacent branches of the hepatic artery. In other words, it is possible that the flow through the interlobular portal venules is largely dependent upon the degree of turges-

[1] Burton-Optiz: Quarterly Journal of Experimental Physiology, 1910, iii, 297.
[2] Burton-Optiz: ibid., 1913, vii, 57.

cence of Glisson's capsule, which again will depend upon the caliber of the hepatic arterioles.

That the hepatic blood flow may influence that of the portal vein seems to have been first of all suggested by Gad. Burton-Optiz calls attention to this work, but he himself rather insists upon the opposite relationship, namely, "that the hepatic inflow may become a highly important compensatory factor whenever the portal inflow is lessened or entirely obstructed."[3] As we shall see later, however, certain of the results of this investigator could be explained on the above basis.

To put the hypothesis, that the pressure in the hepatic artery influences the portal flow, to the test was one of the objects of this research, the others being to supply futher data regarding the relative magnitude of the portal and hepatic moieties of blood supply. In the recent work of Burton-Optiz, which has furnished us with most valuable information on this latter point, the measurements were made by attaching stromuhrs to either the hepatic artery or the portal vein. Apart from the possible interference with blood flow or blood pressure produced by inserting the stromuhr, simultaneous measurements on both vessels cannot be made conveniently, and it is only by comparison of results independently taken on the two that conclusions can be drawn regarding the influence of the one blood flow on the other. In the present investigation, we have, therefore, measured not the inflow but the outflow of blood, and we have observed the effect produced on this by various experimental procedures which might furnish data relative to the above questions.

In choosing experimental procedures by which the flow in one vessel might alone be altered so that changes in the other could be observed, we are distinctly limited. Ligation of the hepatic artery will of itself fail to furnish us with the necessary information, because the sudden removal of the turgescence in the capsule of Glisson is likely to be followed by an immediate and maximal dilatation of the portal venules, so that the net effect on the outflow will be the difference between the withdrawal of the he-

[3] Burton-Optiz: ibid., 1911, iv, 93.

patic artery inflow and the compensatory increase in the portal inflow, if such should occur. Not knowing what proportion of the normal inflow is portal, one cannot, therefore, tell from outflow measurements whether it has undergone any increase. Obviously the only way to do this by measurement of inflow would be to compare the portal flow before and after ligation of the hepatic artery. So far as we are aware, this has not been done, but even if it had been, the results would be open to the criticism that the inflow of portal blood was more or less interfered with by the insertion of the stromuhr.

In the present research we have, therefore, studied the outflow of blood from the liver before and during stimulation of the hepatic plexus, in the hope that although the nerve influence is exerted on both groups of vessels, it would be so feebly on the portal venules, that these would undergo dilatation when the turgescence in the capsule of Glisson is lessened by diminished arterial inflow.

To control the results obtained by the above experiments, we have also studied the local influence of adrenalin on the liver outflow. This has proved a most difficult thing to do satisfactorily for reasons which will be set forth later on.

Observations have incidentally been made on the relative magnitude of the blood flow by way of the portal vein and hepatic artery respectively, and on several other points of general interest.

METHODS

The animals varied in size between about 10 and 20 kgm. After being anesthetized with ether and tracheal and carotid cannulae inserted, the abdomen was opened and the renal vessels ligated, including the adrenal (transverse lumbar) vein on the left side. The aorta was ligated well below the coeliac axis and a wide cannula inserted in the central end of the vena cava. The hepatic plexus was then carefully separated from the hepatic artery, and this was ligated beyond the point at which the hepatic branches leave it. The further preparation of the liver vessels, etc., depended on the nature of the experiment and requires no

special description here. A cut about 2 inches long was then made between the ninth and tenth ribs, and after prying these apart, a thread was placed around the vena cava just above the diaphragm. By pulling on this thread, the vein becomes entirely obliterated. Breathing was very slightly interfered with by these operations, but it became perfectly normal in a minute or so after the wound in the thoracic wall had been closed.

The operations being completed, a receiving vessel was attached to the cannula in the vena cava and connected by tubing with a volume recorder as described by one of us—R.G.P.—in a previous communication. To measure the blood flow a clamp placed on the tube of the recorder was removed at the same time that the ligature around the vena cava was pulled on. As soon as sufficient blood had collected in the receiver to operate the signals, the ligature around the vena cava was again loosened, and the receiver tilted up so that the blood flowed at low pressure back into the circulation. It was found that any attempt to accelerate the emptying of the receiver, by means of pressure, was likely to paralyze the right heart and cause a fatal lowering of blood pressure. Clotting was prevented usually by placing some leech extract in the receiver and by coating this with hard paraffin.

Because of the presence of minute inaccessible lumbar veins emptying into the vena cava just below the hepatic veins, some of the blood which collected in the receiver had not really traversed the liver. Being inconstant in amount, it has been impossible for us to allow for this in our experiments, but we believe that the error thus incurred does not affect the main conclusions which we have drawn.

RESULTS

1. The magnitude of the combined flow

This may be taken as the average flow in cubic centimeters per second measured at the beginning of each experiment. The average of the three separate determinations which immediately precede whatever experimental condition was to be studied, is calculated. Of the observations suitable for such compilation, table I gives the results.

Omitting for the present experiment 17, the minimum flow was 4.16 c.c. per second to the maximum 8.9, the average for ten observations being 6.51. In several of the observations the liver was weighed after death and the flow calculated per 100 grams of liver substance, the average being 1.59, which is somewhat higher than that given by Burton-Opitz,[4] namely, 1.4. The figures from which this average is computed, however, vary considerable. The greater flow observed by us may be explained by the fact that the discharge of a few minute lumbar veins is included. But sometimes, and for no obvious reason, the flow may vary greatly from the above values; thus in experiments 14, 15 and 17, it

TABLE I

EXPERIMENT	AVERAGE FLOW PER SEC.	PER 100 GRAM LIVER	ARTERIAL BLOOD PRESSURE	WEIGHT OF DOG	WEIGHT OF LIVER
	cc.		*mm. per kgm.*	*kgm.*	*gram*
4	6.21		130-150		
6	7.63		130		
10	6.58	1.68	175	8.6	390
11	4.16	1.34	110	9.7	310
12	5.75	1.53	140		373
13	5.45	1.18	140	8.3	290
14	8.9	2.40	11	6.3	375
15	8.5	2.36	150	9.6	370
16	5.8	1.06	140	10.9	490
17	12.5	2.27	160	14.2	550
18	8.3	1.22	160	17.4	680

amounted to 8.9, 8.5, and 16.3 c.c. per second respectively. We are at a loss to explain these abnormally rapid flows. In one of them, viz., that of experiment 17, the vessels of the intestines were markedly dilated. This may have been the case in 14 and 15. In one or two experiments the flow was apparently much lower than above the minimum at the start, but its subsequent acceleration to about the normal probably indicated an incomplete obliteration of the vena cava in the thorax.[5]

[4] Burton-Optiz: ibid., 1911, iv, 113.

[5] A very marked increase in outflow often occurred when the arterial blood pressure became markedly depressed as a result of too much anaesthetic. We can at present offer no explanation for the result.

2. The magnitude of the outflow with either the hepatic artery or the portal vein clamped

Comparisons between the outflow when one or other vessel is clamped, and the total outflow, give us approximately the relative contribution of either vessel. Partly on account of minute lumbar veins which open into the vena cava just below the hepatic veins and partly because of collateral circulation, a certain amount of blood continues to flow after clamping both vein and hepatic artery (Table II). Theoretically it should be possible to allow for this in our calculations, but practically it is impossible

TABLE II

Blood flow into vena cava in cc. per second after clamping the entire hepatic pedicle (Blood Pressure in brackets)

EXPERIMENT	BEFORE CLAMPING	DURING CLAMPING	REMARKS
9	8.75 [70]	1.2 [8]	Immediately preceding clamping of pedicle
	5.39 [70]	0.8 [80]	
	6.00 [70]	1.0 [70]	
		0.7 [60]	
16	5.6 [60]	0.504	Immediately preceding clamping of pedicle
	5.8	0.324	
		0.396	
17	12.1 [140]	1.80 [100]	Flow earlier in experiment
	13.3 [140]	1.08 [80]	
	12.1 [140]	0.297 [50]	

to do so because of its irregularity when measured under the above conditions. The shrinkage of the previously distended liver, thus allowing some outflow to continue after clamping, the fall of blood pressure due to stagnation in the splanchnic vessels, and the possibility that the same number of lumbar veins are not discharging into the cava in all the experiments, explain the irregularities. Although in many of the experiments attempts were made to obliterate the lumbar veins by mass ligation, it was found difficult to be certain that they were all obliterated.

(*a*) *The effect of clamping the hepatic artery.* After making several observations on the normal flow, the main branch of the hepatic artery central to the point from which the hepatic branches originate was obliterated either by applying a clamp or by

TABLE III

Blood flow from liver in c.c. per second as affected by clamping the hepatic artery (Blood Pressure in brackets)

EXPERIMENT		IMMEDIATELY PRECEDING OBLITERATION	DURING* OBLITERATION	FOLLOWING OBLITERATION	AVERAGE DECREASE		REMARKS
					cc.	*per cent*	
3		10.00 10.00 9.3	6.64 7.3 6.05 6.95 5.84	6.2 9.13 6.2 8.1			Hep. art. not tied beyond liver
	Average.	9.75	6.55	7.4	3.2	33	Observation followed others made of effect of stim. of hep. plexus
5		9.53 9.10	8.20 7.75 8.20	11.25 9.10 11.25			Abnormally high rate of flow
	Average.	9.31	8.05	10.53	1.26	13.5	Observation made late in exp.
6		8.24 8.24 8.24	[7.94] 6.35 7.33	 10.6 9.53			Late in experiment. Abnormally high rate of flow
	Average.	8.24	6.84	10.06	2.40	2.91	
11		4.28 4.05	3.07 3.00 2.70 2.80				Unusually slow rate of flow
	Average.	4.16	2.89		2.27	54	
12		5.75 [140] 5.75 5.75 [90]	[140] [90]	4.5 [140] 4.5 4.5 [90]			
	Average.	5.75	3.94	4.5	1.81	31.4	
	Per 100 gram liver	1.53	1.02	1.20			

TABLE III—Continued

	EXPERIMENT	IMMEDIATELY PRECEDING OBLITERATION	DURING* OBLITERATION	FOLLOWING OBLITERATION	AVERAGE DECREASE		REMARKS
					cc.	per cent	
12	Liver 5 minutes later	4.5 [140] 4.5 4.5 [90]	3.15 3.80				
	Average.	4.5	3.32		1.18	26	
	Per 100 gram liver	1.21	0.89				
12	Liver 10 minutes later	8.4 [100] 8.4 8.4 [60]	5.73 5.73				This increased flow late in exp. is a very common occurrence
	Average.	8.4	5.73	7.97	2.67	31.7	
18		9.0 [160] 8.3 8.3	6.79 [160] 7.83 5.72 5.3				
	Average.	8.5	5.9		2.6	30	

tightening a thread. In most of the experiments the main artery was also ligated beyond these branches.

The effect which obliteration of the hepatic artery has on the outflow seems to depend considerably on the condition of the animal at the time that the observation is made. In our earlier observations this particular experiment was not undertaken until after several others had been performed on the same animal, with the consequence, as already stated, that the flow was abnormally rapid and quite irregular. In two of these experiments (3 and 6), sufficiently constant results were, however, obtained, the hepatic artery moiety being respectively 33 and 29.1 per cent of the total flow. In another of this series, also showing a rapid flow, the hepatic moiety was only 13.5 per cent. In observations 12 and 18 the above experiment was the first one performed, and the results showed from 26 to 31.7 per cent of the blood to

be derived from the hepatic artery. In experiment 11, the diminution following clamping was 54 per cent, but the abnormally small initial flow in this case indicates a probable interference with the portal flow, although no cause for this could be discovered.

As a general average, we are probably safe in concluding that from 26 to 32 per cent of the blood which flows through the liver is derived from the hepatic artery. In other words, about one-third of the blood in the liver is arterial. Inasmuch as the hepatic artery is richly supplied with vasoconstrictor nerve fibers, the blood flow through it is subject to very considerable variations and consequently the ratio between the flow in it and in the portal vein may undergo alterations from time to time. It is probably on account of such changes that the unusual values, such as in experiments 5 and 11, are to be explained. To control this factor the observations should be repeated with the vasomotors paralyzed.

(*b*) *The effect of clamping the portal vein.*

These observations sufficiently corroborate those made by clamping the hepatic artery, for they show that the outflow is diminished by about two-thirds by clamping the portal vein. The unusually small decrease in the first observation of XVIII was probably due to faulty application of the clamp.

Although the above conclusion merely confirms that of Burton-Optiz, who found the hepatic artery to contribute from 24 to 44 per cent of the total flow, yet it seems to us important to have been able to confirm it by measurements which entail no sort of disturbance on the ingoing blood vessels. The minute size of those branches of the hepatic artery which actually enter the liver as compared with the enormous size of the portal vein would lead one to expect a much larger contribution of blood through the latter vessel even although the pressure differences in the two vessels are very great. The result explains why it is that deflection of the portal flow into the vena cava (Eck fistula) should ordinarily create no very marked metabolic disturbance. By still retaining from one-fourth to one-third of their normal flow (through the hepatic artery) the liver cells can perform their functions sufficiently to prevent a serious accumulation of such

TABLE IV

Blood flow from liver in c.c. per second as affected by clamping portal vein. (Blood Pressure in brackets)

EXPERIMENT		IMMEDIATELY PRECEDING OBLITERATION	DURING OBLITERATION	FOLLOWING OBLITERATION	AVERAGE CHANGE	
					cc.	*per cent*
IX		5.25 [100] 5.15	1.87 [100] 1.87 [80]	4.20 [80] 4.10 [80] 4.56		
	Average.....	5.20	1.87	4.30	3.00	64
IX Continued		4.20 [80] 4.10 [70] 4.56 [80]	2.00 [70] 2.20 [70] 1.69 [60]	8.75 [60] 5.39 [70] 6.00 [70]		
	Average.....	4.30	1.96		2.34	54
XVIII		8.30 [120] 8.30 8.25	4.60 [120] 6.70	[6.54] 7.2 8.25		
	Average.....	8.30	5.56	7.70	2.74	33
XVIIa		7.20 [120] 8.25	2.50 [80] 2.76 2.88			
	Average	7.7	2.70		5.00	64

substances as ammonia, monosaccharides, etc., in the systemic blood, unless excessive amounts of these substances are being absorbed from the intestine.

3. The effect of stimulation of the hepatic plexus on the outflow.

For purposes of stimulation the entire hepatic plexus was cut and the peripheral end carefully laid on guarded electrodes connected with a standard Rhumkorff coil of 10,000 windings, the secondary being placed either at 4 or 6 cm. from the primary. The stimulation did not have any effect on the respiratory movements; any slight effect which, as Burton-Opitz found, it might have on arterial blood pressure (with untied hepatic arteries) was

masked in our experiments by the slight fall which occlusion of the vena cava entailed.

The invariable result (cf. Table V) was an immediate acceleration in the blood flow, followed after a period of a few seconds by a return to the normal. The extent and duration of this increased flow were somewhat inconstant; the former varied from about five per cent in experiment 1, to sixty per cent in experiment 3, the latter, from 5 seconds (or less) in experiments 2, 4 and 6 to 15 seconds (or more) in experiments 8 and 10. This initial acceleration is no doubt to be attributed to a squeezing out of blood in the liver as a result of vasoconstriction. This constriction affects the branches of the hepatic artery much more than those of the portal vein, for it affects both the volume flow and the pressure in the hepatic artery, while the constriction of the portal venules, although it raises the portal pressure, causes no measureable change in portal flow.[6]

The subsequent return to the normal flow indicates either that the constriction does not last for long, or that it persists, but is accompanied by a compensatory increase in flow through the portal vein. In view of the fact that Burton-Opitz found constriction of the hepatic artery to persist at least as long as the hepatic plexus was stimulated, we are forced to accept the latter as the correct interpretation, namely, that a compensatory or reciprocal increase in portal flow occurs.

Since, as already mentioned, this author could not detect any change in portal flow when the peripheral end of the hepatic plexus was stimulated, although he was able to observe a rise in portal pressure, it follows that the compensatory increase in the outflow in our experiments cannot be due to an active vasodilation of the portal radicles, but to their passively opening up on account of a lower pressure in the neighboring arterioles. This tendency to open up which results from the removal of the arterial turgescence must be greater than the constriction of the vessels resulting from stimulation of the hepatic plexus. The tissues of the capsule of Glisson must act somewhat in the manner of

[6] Burton-Optiz: ibid., 1913, vii, 57.

TABLE V

The effect of stimulation of the hepatic plexus on the outflow of the liver. (*Blood pressure in brackets*)
Blood flow in cubic centimeters per second

EXPT.	NORMAL	DURING STIMULATION OF PLEXUS	NORMAL	DURING STIMULATION OF PLEXUS	NORMAL	DURING STIMULATION OF PLEXUS	NORMAL	DURING STIMULATION OF PLEXUS	REMARKS
2	3.38 [120]	3.38 [125]	3.38 [125]						Coil of 4 cm. No change in Blood pressure.
	3.75 [120]	4.82 [125]	3.75 [125]						
	3.95 [120]	3.75 [125]	3.59 [125]						
		3.75 [125]							
		3.38							
3	5.84 [134]	9.75 [134]	5.62 [150]	9.75 [150]	8.10 [110]	8.10 [130]	12.10 [130]	14.60 [80]	Coil 6 cm. A marked acceleration in the flow is noticeable later in the experiment.
	6.20 [140]	9.75 [134]	5.04 [150]	9.75 [150]	5.40 [110]	9.13 [130]	12.10 [130]	9.74 [100]	
	5.84 [140]	9.75 [140]	6.64 [150]	6.95 [150]	6.09 [110]	9.13 [130]	10.00 [130]	12.10 [100]	
		6.64 [150]	6.20 [150]	6.95 [116]	6.95 [122]	12.10 [130]	10.00 [130]	12.10 [100]	
		5.84 [160]	7.67 [150]	6.95 [110]	5.84 [120]	10.00 [130]	8.10 [130]		
		5.84 [150]		6.95 [110]	8.10 [130]	10.00 [130]	10.00 [100]		
					8.10 [134]		14.60 [100]		
							14.60 [100]		
							12.10 [100]		
4	6.84 [130]	9.83 [140]	7.15 [140]	7.49 [130]	6.20 [160]				Coil 4 cm.
	5.83 [140]	7.15 [150]	6.06 [120]	7.49 [140]	6.55 [120]				
	6.56 [140]	7.15 [150]	6.84 [140]	5.43 [150]	6.56 [130]				
				5.42 [160]					
5	12.70 [90]	14.70 [90]	12.70 [96]						
	13.60 [90]	14.70 [90]	8.65 [80]						
	12.00 [90]	12.70 [90]	12.70 [80]						
		13.60 [96]	12.00 [80]						
6	5.74 [60]	7.94 [60]	5.74 [65]						The hepatic a. had been temporarily clamped earlier in the experiment. Strength of stimulant not given.
	6.57 [60]	5.74 [60]	7.33 [66]						
	6.35 [60]	6.57 [60]	6.00 [66]						
		6.57 [60]							
8	2.60 [150]	3.30 [150]	2.70 [150]	3.20 [140]	2.60 [130]				
	2.50 [150]	4.50 [150]	2.40 [150]	3.00 [140]					
	2.50 [150]	3.60 [150]	2.10 [140]	3.00 [140]					
				2.50 [140]					
				2.30 [140]					
10	8.40 [160]	10.50 [180]	7.16 [170]	10.00 [170]	5.20 [170]	9.14 [180]	4.77 [170]		The marked irregularity in flow could not be explained.
	6.17 [180]	8.40 [180]	7.30 [170]	8.73 [180]	6.90 [170]	8.10 [180]	4.77 [170]		
	5.10*[180]	10.00 [180]	7.60 [170]	8.40 [180]	8.40 [180]	8.10 [180]	4.50 [170]		
		30 sec. rest		30 sec. rest					
		9.14 [170]		7.16 [170]		7.16 [180			
		7.16 [180]		8.72 [170]		8.72 [180]			
				8.72 [170]		6.20 [170]			
				7.16 [170]		5.10 [170]			

*Irregular flow makes magnitude of increase somewhat uncertain.

erectile tissue; with a normal inflow through the hepatic artery this tissue must exercise a certain compression on the portal radicles, but when the arterial inflow is cut down, the latter vessels must open up and permit more blood to flow through them. That this passive dilatation of the portal radicles does not entail an initial fall in total outflow—because of a temporary stagnation in the (portal) blood flow—is to be explained by the fact that the blood, which has already gained the hepatic lobule itself is not affected by the diminution in turgescence in the interlobular tissues; it flows on, but has added to it the blood which has been pressed out of the hepatic arterioles as a result of their constriction.

Although there is at present no other evidence than the above that such a compensatory increase in the portal venules does occur, it is of interest to note that Burton-Opitz has found the hepatic artery to be become dilated when the portal blood flow is made to cease by deflecting it into the renal vein.

There are, however, certain observations of this author[7] which although interpreted by him in another way may yet as well be attributed to a passive dilatation of the portal venules. Thus it was found that the portal flow became greater when the hepatic plexus was stimulated. Since this increased flow was much more marked when the plexus was uncut, it was attributed to the reflex rise in the arterial blood pressure, which under these conditions is quite distinct. Such an explanation cannot account for the increase which, although much less marked, is stated to have occurred when the peripheral end of the cut plexus was stimulated. Burton-Opitz attributes this also to a general rise in blood pressure resulting from constriction of the hepatic artery in the liver. It may, however, be due to a passive dilatation of the portal venules.

We have also studied the change which is produced in the outflow when the hepatic plexus is stimulated after ligation of the hepatic artery. Table VI gives the results.

It is seen that a very slight, if any, increase in outflow occurred when the plexus was stimulated with ligated arteries. Where

[7] Burton-Optiz: ibid., 1911, iv, 113.

present it was very transient, and is no doubt to be explained by a squeezing out of the blood in the hepatic arteries, or possibly in the portal venules. That there is no permanency in the increased outflow in the experiment as compared with those of the previous group indicates that the portal venules were fully dilated from the beginning, the arterial tension being low because the arteries were ligated.

TABLE VI

The effect of stimulation of the hepatic plexus on the outflow of blood from the liver after ligation of the hepatic arteries. (Figures represent c.c. per second, mean arterial blood pressure in mm. Hg in brackets)

EXPERIMENT	BEFORE STIMULATION	DURING STIMULATION	AFTER STIMULATION
VIII	8.10 [100]	7.10 [100]	4.00 [90]
	7.20 [100]	7.10 [100]	4.40 [90]
		5.00 [90]	5.50 [90]
			5.20 [90]
VIIIa	5.50 [90]	5.00 [80]	
	6.30 [90]	6.80 [80]	
	5.20 [90]	5.00 [80]	
XI	3.07 [110]	3.40 [110]	2.73 [100]
	3.00 [110]	3.00 [110]	2.36 [100]
	2.70 [110]	2.85 [110]	
	2.80 [110]	3.00 [110]	
IXa	2.73 [100]	3.20 [100]	2.80 [100]
	2.63 [100]	3.00 [100]	2.50 [100]

The action of adrenalin on the hepatic blood flow

These experiments were undertaken partly to furnish further evidences for or against the above hypothesis concerning the effects of stimulation of the hepatic plexus, and partly to find out to what extent constriction of the portal venules might curtail the outflow of blood. The adrenalin was injected in quantities of 2 cc. of either 1-10,000 or 1-5,000 in the pancreatic duodenal vein, it having been shown that this amount of saline does not by itself cause any appreciable change in the outflow. Larger amounts of saline were found to increase the outflow, probably because of diminution in the viscosity of the blood. Any changes in the blood flow due to the rise in general arterial blood pressure are

discounted in our experiments because the outflowing blood was either collected in a large receiver and not permitted to enter the heart until several measurements had been taken, or the small receiver was used but quickly emptied and another measurement made before the adrenalin had affected the arterial blood pressure. The observations were made with and without ligation of the hepatic arteries. Table VII gives the results.

In practically every instance, whether with or without ligation of the hepatic arteries the adrenalin produced a definite diminution in outflow. We have already alluded to the fact that although Burton-Opitz succeeded in showing that a rise in portal blood pressure occurred after the injection of adrenalin into the portal vein, yet he could not make out, by stromuhr measurements of the portal inflow, that this had suffered any curtailment. The present results are therefore mainly of interest in that they supply such evidence. Apart from the difference in technique of our experiments as compared with those of Burton-Opitz, it is important to note that we injected about twice as much adrenalin as this author. We believe that similar results would be obtained with smaller injections. It will be noted that a few of our observations (viz., XII, XVIa and XVIIa) show a slight increase in outflow as the first effect of the adrenalin injection. This increase in outflow is probably due to a squeezing out of blood from the venules, but it is too inconstant, and, when present, too insignificant to make its presence or absence a distinguishing feature between adrenalin constriction of the venules and nervous constriction of the arterioles, where the initial acceleration is so marked a feature.

It will be noted that the diminution in outflow, both absolutely and relatively, was usually much more decided when the hepatic arteries were intact than when the only blood supply to the liver was through the portal vein. The observations were divided into these two groups in the hope that some clue might be furnished indicating the exact locus of action of adrenalin, i.e., whether on the portal venules central to their union with the branches of the hepatic artery, or beyond this point. In the former case, we should expect the relative diminution in outflow, as a

TABLE VII

The local effect of the injection of adrenalin (2 cc. of 1 to 10,000) on the outflow of blood from the liver. (Figures represent cc. blood per second; mean arterial blood pressure in brackets)

A. With intact hepatic arteries

EXPERIMENT	BEFORE ADRENALIN	DURING ACTION OF ADRENALIN	CHANGE IN FLOW	
			cc.	*per cent*
XIV	9.30 [110 mm.]	8.80 [110 mm.]		
	8.80 [110 mm.]	5.56 [130 mm.]		
	8.80 [110 mm.]	6.00 [130 mm.]		
Average.....	8.9	6.80	−2.10	−25.0
XIVa	8.00 [60 mm.]	7.50 [60 mm.]		
	9.30 [60 mm.]	5.00 [80 mm.]		
		3.50 [80 mm.]		
Average.....	8.65	5.30	−3.35	−38.0
XV	8.55 [150 mm.]	4.16 [150 mm.]		
	8.55 [150 mm.]	3.60 [150 mm.]		
		3.24 [150 mm.]		
Average.....	8.35	3.66	−4.89	−57.0
XVa	6.84 [150 mm.]	3.96 [150 mm.]		
		3.60 [150 mm.]		
		4.95 [150 mm.]		
Average.....	6.84	4.17	−2.67	−39.0
XVI	5.85 [140 mm.]	5.94 [140 mm.]		
	4.77 [140 mm.]	6.93 [140 mm.]		
	5.13 [140 mm.]	6.75 [140 mm.]		
Average.....	5.25	6.54	−1.29	−24.0
XVIa	7.38 (140 mm.]	9.00		
	7.38 [140 mm.]	6.30 [140 mm.]		
	7.65 [140 mm.]	6.90		
Average.....	7.45	7.40	−0.06	
XVIb	6.12 [140 mm.]	5.49 [140 mm.]		
	5.67	4.68		
	5.67	6.12		
Average.....	5.82	5.42	−0.40	−6.0

TABLE VII—Continued

EXPERIMENT		BEFORE ADRENALIN	DURING ACTION OF ADRENALIN	CHANGE IN FLOW	
				cc.	*per cent*
XVII		10.20 [160 mm.]	11.20		
		11.20 [160 mm.]	8.10 [160 mm.]		
		11.20 [160 mm.]	6.50 [160 mm.]		
	Average.....	10.90	8.61	−2.29	−22.0
XVIIIa		10.90 [140 mm.]	11.25 [140 mm.]		
		12.00 [140 mm.]	9.72 [140 mm.]		
		10.90 [140 mm.]	8.50 [155 mm.]		
			7.60 [155 mm.]		
	Average.....	11.20	9.29	−1.91	−17.0
	B. With ligated hepatic arteries				
XII		7.90 [100 mm.]	8.40 [120 mm.]		
		7.00 [100 mm.]	6.30 [120 mm.]		
		6.00 [60 mm.]	5.10 [100 mm.]		
			(15 sec. interval)		
			5.73 [120 mm.]		
			5.73 [100 mm.]		
	Average.....	7.00	6.60	+0.40	−5.6
XIV		3.75 [60 mm.]	4.69 [60 mm.]		
			4.20 [60 mm.]		
			4.30 [60 mm.]		
	Average.....	3.75	4.39	+0.64	+17.0
XVI		4.59 [120 mm.]	3.69 [120 mm.]		
		4.59 [120 mm.]	4.59 [120 mm.]		
			4.14 [120 mm.]		
			4.05 [120 mm.]		
	Average.....	4.59	4.12	−0.47	−10.0
XVIa		6.04 [120 mm.]	3.33 [100 mm.]		
		4.77 [120 mm.]	4.50 [100 mm.]		
			3.87 [100 mm.]		
			4.78 [100 mm.]		
	Average.....	5.40	4.12	−1.28	−23.0

TABLE VII—Continued

EXPERIMENT		BEFORE ADRENALIN	DURING ACTION OF ADRENALIN	CHANGE IN FLOW	
				cc.	*per cent*
XVIb		5.13 [60 mm.]	2.97		
		4.50	3.33		
		4.41	5.04		
	Average.....	4.68	3.76	−0.92	−20.0
XVII		8.10 [140 mm.]	5.67 [140 mm.]		
		9.70 [140 mm.]	5.94 [140 mm.]		
		7.20 [140 mm.]	4.86 [140 mm.]		
	Average.....	8.30	5.82	−2.48	−30.0
XVIIa		4.86	6.39		
		6.66	6.21		
			4.50		
			6.84		
	Average.....	5.76	5.96	+0.20	+4.0

Average decrease in blood flow on injection of adrenalin into portal vein with intact hepatic arteries, 22.0 per cent.

Average decrease in blood flow on injection of adrenalin into portal vein with hepatic arteries ligated, 10.5 per cent.

result of adrenalin injection, to be greater when the hepatic artery is tied than when it is patent. That the opposite should actually be the case probably means that the adrenalin, although injected into the vein, acted most strongly on the hepatic arterioles, with which it was brought in contact by eddying of blood into them. Being very richly supplied with vasomotor nerves, the arterioles are so sensitive to adrenalin that the smallest trace can cause them to constrict to a relatively greater degree than a much larger dose acting directly on the portal venules.

On account of the irregularity in our results in this regard, we do not desire to insist on the above differences between the groups of observations as of much significance. We think, however, that we are warranted in the conclusion that the constriction cannot be confined to the portal venules before they join with the hepatic arterioles.

That adrenalin should cause a diminution in liver outflow, and stimulation of the hepatic nerves should not do so, when the hepatic artery is ligated (cf. Table VI) indicates that the vasomotor supply to the venules must be very feeble.

CONCLUSIONS

1. The total outflow of blood from the liver of the dog varies between 1.06 and 2.40 cc. per second and 100 grams of liver. There is only a very general relationship between the magnitude of the flow and the mean arterial blood pressure.

2. Even after the vessels of the hepatic pedicle have been clamped, blood still collects in the vena cava. Part of this comes from minute lumbar veins; the remainder may be due to collateral circulation.

3. Occlusion of the hepatic artery usually causes the outflow to diminish by about 30 per cent, but since the exact ratio between the flow in the portal vein and the hepatic artery will depend on the extent to which these vessels are under vasomotor control at the time of observation, the diminution may be considerably greater or less than 30 per cent.

4. Occlusion of the portal vein usually diminishes the outflow by about 60 per cent.

5. Stimulation of the peripheral end of the cut hepatic plexus, with both artery and vein intact, causes an immediate increase in the outflow, after which this returns approximately to its original amount. This return to the normal flow is explained as due to a passive dilatation of the interlobular portal venules resulting from a lowering of the arterial tension in the capsule of Glisson.

6. The changes in outflow following stimulation of the hepatic plexus are very much less marked, or absent altogether, when the hepatic artery is ligated.

7. Injection of adrenalin (2 cc. of 1 in 10,000) into the portal vein causes an immediate decrease in the outflow. This result is practically the same with unligated as with ligated hepatic arteries. It indicates that the ramifications of the portal vein in the liver are supplied with vasoconstrictor nerve fibers. Since a similar diminution did not occur when the hepatic plexus was stimulated, the portal vasomotor nerve fibers must be very feeble.

THE OXYGEN PULSE AND THE SYSTOLIC DISCHARGE

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By the term "oxygen pulse" we mean the amount of oxygen consumed by the body from the blood of one systolic discharge of the heart. Its value is calculated by dividing the amount of oxygen absorbed by the individual per minute by the number of heart beats in the minute. The oxygen pulse must be clearly distinguished from the total amount of oxygen in the blood of one systolic discharge. For instance, if the left ventricle effects a tidal volume of 100 cc. of blood, the volume of oxygen contained in it is (for an individual with 100 per cent haemoglobin according to the Gower-Haldane scale and measured at standard pressure and temperature) 18.5 cc. If at the same time the blood is returning to the right heart still carrying 16 volumes per cent of oxygen, the oxygen pulse is 2.5 cc.

This conception is one which has entered into many important and well known investigations,[1] but owing to the lack of a name and definition it has not received the attention which its importance and ease of determination warrant. It is the oxygen pulse which more than any other factor determines the total energy which a man can command for the most strenuous moments of life. Its maximum value depends upon the haemoglobin index and the tidal volume of the heart.

Determinations of the oxygen pulse have an important bearing on the problems of the tidal volumes of the heart, the total circu-

[1] For a discussion of this topic and full references to the literature see Murlin and Greer. This journal, 1914, xxxiii, 253.

lation per minute, and related questions. But while the systolic discharge of the left ventricle in man is (with all due respect to the various methods which have been proposed for its estimation) a quantity which can only be roughly guessed at, the oxygen pulse is an easily and exactly measurable function. By either of two excellent methods for obtaining the total respiratory exchange —one devised by Benedict[2] and the other by Douglas[3]—it may be determined on healthy men at rest or during exercise, even the most vigorous, on fever patients and on persons with cardiac diseases.

All of the observations to be reported in this paper were made on healthy men. The heart rate and oxygen consumption were varied by adjusting the amount of physical exertion. Thus observations were made with the subject at rest in bed, seated in a chair, standing, seated on a stationary bicycle, and doing moderate and hard pedalling.[4] The pulse rates were counted either from the temporal artery or more conveniently by means of a stethoscope with a large bowl over the apex of the heart. In the observations during exercise the observer was usually able, by merely directing the subject to pedal a little faster or slower, to keep the heart at the desired rate of beat within a variation of not more than five beats to the minute. The subject counted his own respiration.

In our preliminary observations we determined the respiratory exchange by means of a gasometer and a large tin of soda lime. From the mouthpiece, through which the subject breathed, the expired air passed through a mica valve and large corrugated rubber tube to the soda lime tin, where the CO_2 was absorbed, and thence into the gasometer. Another tube and mica valve connecting the gasometer directly to the mouthpiece provided for inspiration. The movements of the gasometer were recorded on a smoked drum and showed the rate and amplitude of the breathing.

[2] Benedict, F. G.: This journal, 1909, xxiv, 345.

[3] Douglas, C. G.: Journal of Physiology, 1911, xlii, 17.

[4] A simple and convenient bicycle ergometer has recently been described by Martin C. J.: Journal of Physiology, 1914, xlviii, p. xv. Our apparatus was similar although not so good.

At the beginning of the experiment and at intervals thereafter, the gasometer was filled with oxygen from a tank of compressed gas. As the subject consumed the oxygen, the gasometer gradually sank and the graphic record thus obtained afforded a means of measuring the consumption. Such an arrangement, in effect a crude form of the so-called "small Benedict apparatus,"[5] is quite useful for many purposes. Its principal drawbacks are that during hyperpnoea there is a perceptible resistance, and that when the air passes through the soda lime very rapidly the absorption of CO_2 is liable to be incomplete. It determines only the oxygen consumption, not the CO_2 output.

Mention may here be made of an absorption apparatus devised by one of us (Y. H.) in collaboration with Prof. J. M. Flint, which to a great extent overcomes these drawbacks. It consists of a cylindrical glass vessel of about 4 liters capacity with an opening of 4 cms. diameter

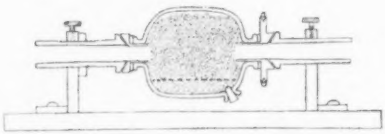

Fig. 1. Rotating absorber for CO_2.

at each end. It is filled with pumice in pieces 0.5 to 1.5 cms. diameter, and is supported on its side in a frame so that it can be rotated on its long axis. Enough strong KOH solution is poured in to moisten all of the pumice and provide an additional 300 to 500 cc. of free liquid which pours over the pumice when the jar is rotated. The pipes connecting with it at each end must have accurately ground bearings. The jar may be kept in continuous, slow rotation by means of a small motor, and will then absorb CO_2 from even a rapid current of expired air down to a small fraction of 1 per cent. With ordinary rates of breathing, the jar need only be turned by hand once in three to five minutes and gives a nearly perfect absorption. The jar should have a small opening on the side, closed by a rubber stopper, so that the potash solution may be easily renewed. The construction of the device is shown in figure 1.

[5] Benedict: loc. cit.

Most of our observations, however, were made with the "Douglas bag."[6] This apparatus is much simpler and easier to use, more accurate, and affords more nearly normal conditions as regards the air breathed by the subject, than any other respiratory device with which we are acquainted. It is equally adaptable to all conditions,—laboratory, bedside, race-track or mountain peak. It consists merely of a nose clip, a mouthpiece with an inspiratory valve through which the air is inhaled, and an expiratory valve through which the subject exhales into a large rubber bag carried on his back. The time required to fill the bag is noted; the volume is afterwards measured by means of a gasometer, and a sample is analyzed for oxygen and CO_2.

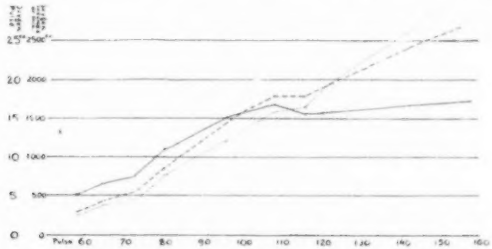

Fig. 2. Subject Y. H., Weight 75 kilos. Haemoglobin 107. In this and succeeding diagrams the broken line expresses the oxygen consumption per minute, the dotted line the CO_2 elimination, and the solid line the oxygen pulse. During the short periods of vigorous exertion and rapid heart rates, the CO_2 elimination was increased to a greater extent than the oxygen consumption, the respiratory quotient even rising above unity in some cases, and indicating an excessive blowing off of CO_2.

The accompanying diagrams (figs. 2 to 11) summarize our experiments. The abscissae express the number of heart beats per minute, while the ordinates show the oxygen consumption and CO_2 elimination per minute on one scale, and the oxygen pulse on the other. In addition to our own results we have plotted data taken from the recent extensive investigations of Benedict and Cathcart.[7]

[6] Douglas: loc. cit.

[7] Benedict and Cathcart: Muscular Work, Carnegie Institution of Washington, 1913.

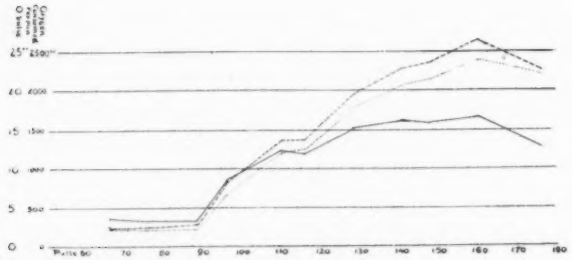

Fig. 3. Plotted from the observations of Benedict and Cathcart (loc. cit.). Subject M. A. M., a professional bicycle rider, unfed. (All of our subjects had taken their ordinary food). The rather surprising parallelism of the curves with the abscissa at heart rates below 88 per minute is due to the fact that the two observations at pulses of 76 and 88 were taken after work when the heart rate was still accelerated, although the gaseous exchange had fallen to a resting value.

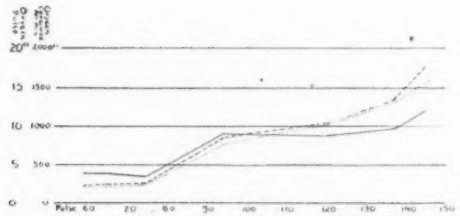

Fig. 4. Plotted from observations of Benedict and Cathcart. Subject J. E. F. Weight 60 kilos.

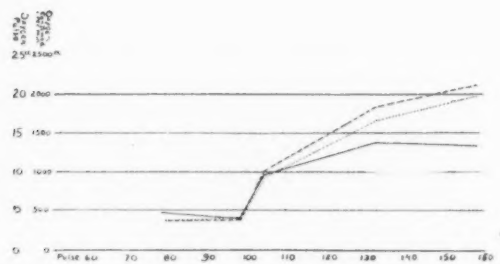

Fig. 5. Subject H. W. G. Weight 99 kilos. This and all the following diagrams are from our own experiments.

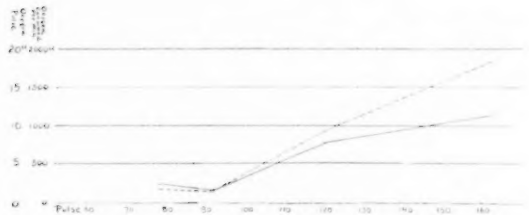

Fig. 6. Subject R. L. S. Weight 62 kilos. Haemoglobin 96

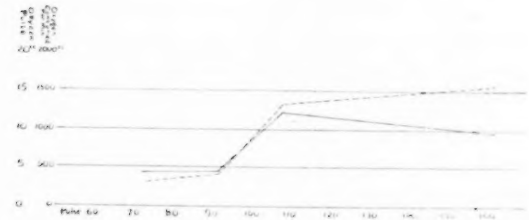

Fig. 7. Subject A. G. H. Weight 73 kilos. Haemoglobin 100

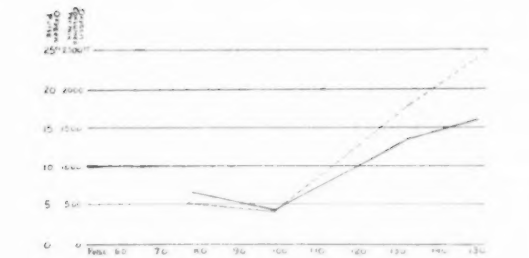

Fig. 8. Subject B.R.L. Weight 57 kilos

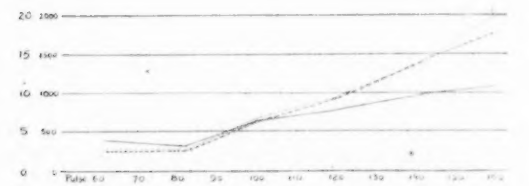

Fig. 9. Subject G. J. G. Weight 65 kilos

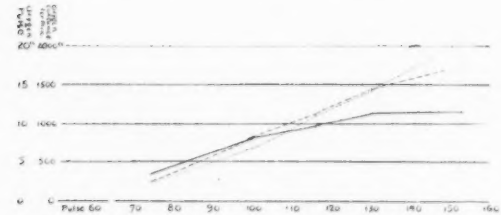

Fig. 10. J. D. R. Weight 68 kilos. Haemoglobin 100

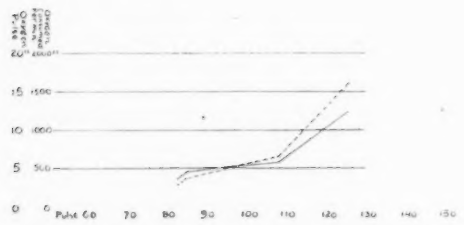

Fig. 11. P. M. Weight 67 kilos. Haemoblobin 102

These diagrams show that the curve expressing the relation of the oxygen pulse to the heart rate is subject to considerable minor irregularities, but tends toward a definite general form. The variations are to be explained by the well recognized fact that many conditions other than the oxygen consumption influence the pulse rate, e.g., high temperature, mental excitement, stimulation of respiration by a high content of CO_2 in the inspired air, etc. In some of the observations taken after exercise the heart rate was still accelerated when the oxygen consumption had fallen practically to a resting value. Any condition which increases the heart rate more than the oxygen consumption decreases the oxygen pulse.

Starting with the slowest heart rates and lowest figures for oxygen consumption it appears that in most persons a slight exertion, involving an increased oxygen consumption of only 20 or 30 per cent over the resting value, causes a nearly proportional acceleration of the heart—the pulse rising from 60 or 70 per minute to 80 or 100. The oxygen pulse remains, therefore,

nearly the same at all such heart rates. This is in accord with recent observations by Murlin and Greer (loc. cit.) on men and on dogs. The values for the oxygen pulse in our various subjects at slow rates of heart beat vary between 2.5 and 6.5 cc., average 4.1 cc., or 0.043 to 0.114 cc. per kilo body weight.

In most subjects a distinct turning point is reached at heart rates between 80 and 100 per minute. From this point onward the oxygen consumption increases in a nearly direct proportion to the cardiac acceleration instead of to the absolute heart rate. Thus on G. J. G., Fig. 9 the oxygen consumption at heart rates of 82, 100, 120, 142 and 160 were 253 cc., 623, 926, 1406, 1759. These figures indicate that the conditions causing the body to consume (in this case) 20 cc. more oxygen per minute produced an acceleration of one beat per minute in the heart rate.

The curves show that from the turning point between 80 and 100 beats per minute the oxygen pulse increases rapidly with physical exertion and acceleration of the heart rate from values of only 2 to 6 cc. up to values of 10 or 15 cc. at heart rates of 130 to 150 per minute. At higher rates it increases only slightly or not at all, and it may even fall. It is probable that when the subject is pushed beyond his powers to extreme tachycardia a considerable fall occurs. The maximum oxygen pulse observed in our experiments was 17.2 cc. on a subject (Y. H.) weighing 75 kilos. The maximum which we have calculated from the observations of Benedict and Cathcart on the professional bicycle rider (M. A. M.) who weighed 65 kilos is 16.6 cc. On the other subjects the body weights and corresponding maximum oxygen pulses were for J. E. F., 60 kilos, 12.3 cc.; H. W. G., 99 kilos, 13.3 cc.; R. L. S., 62 kilos, 11.3 cc., A. G. H., 73 kilos, 12.2 cc.; B. R. L., 57 kilos, 16.0 cc., G. F. G., 65 kilos, 10.8 cc.; J. D. R., 68 kilos, 11.6 cc. and P. M., 67 kilos, 12.6 cc. In general, therefore, the values for the maximal oxygen pulse occurring at heart rates of 130 to 160 beats per minute lie between 10.8 and 17.2 cc.

The primary object of these experiments was to throw some light on the problem of the tidal volume of the heart in man at various rates of beat. With an oxygen pulse of 16 cc. it is evident that the systolic discharge cannot be less (it might be much more)

than 100 c.c. Blood of 100 per cent haemoglobin will only hold 18.5 volumes per cent of oxygen, and it is improbable that the consumption in the tissues is ever so nearly complete that the blood returning to the right heart contains less than 2.5 volumes per cent of oxygen.

If the systolic discharge is 100 cc. in a man while doing hard work and having a heart rate of 150 to 160 per minute, what will it be during heart rates of 60 to 80 per minute? The answer depends upon whether or not the heart under normal conditions obeys the principle of the "superimposability of the volume curve." If it does, it is clear from such indications as we have been able to obtain regarding the probable form of the volume curve of the human heart (to be published in a later paper), that the systolic discharge at rapid heart rates must be only two-thirds of the volume of that at slow rates of beat. At slow rates in a vigorous man of 70 kilos it must then be of about the order of magnitude of 150 to 180 cc., or 2 to 2.5 cc. per kilo body weight. These figure are about twice as large as those commonly adopted as probable in the current text books.

CONCLUSIONS

During bodily rest and with such slightly accelerated heart rates as are involved in merely walking about a room, we find (in agreement with Murlin and Greer) that the quantity of oxygen consumed tends to be proportional to the pulse. The oxygen pulse (defined in the opening paragraph of this paper) under such conditions is, therefore, uniform at values ranging for different individuals between 2.5 and 6.5 cc.

With heart rates such are induced by a distinct exertion and on up to hard muscular work, that is, rates from 80 to 100 per minute up to 130 or 140, a relation between oxygen consumption and heart rate prevails which is altogether different from that above stated. With some exceptions and variations the absolute augmentations are now proportional in such a relation that an increase by a definite amount in the oxygen consumption per minute, varying between 10 and 40 cc. in different individuals, corresponds to an acceleration of one heart beat per minute.

The oxygen pulse at these heart rates, therefore, increases rapidly with acceleration of the rate. In most cases it reaches maximal values of 11 to 17 cc. at rates of 130 to 140 per minute. With further cardio-acceleration it increases only slightly if at all; and it may even tend to decrease.

From these figures we infer that, if no considerable amount of oxygen is consumed in the lungs, the systolic discharge of the left ventricle of a well developed man working hard and with a pulse rate of 140 per minute is not less than 100 cc. of blood. If the normal human heart obeys the principle of "superimposability of the volume curve" the systolic discharge at slow rates of beat is probably 150 cc. or more. In men of poor physique it is probably not more than two-thirds as much. These figures are, however, considerably larger than those which most previous work has indicated.

The expenses of these investigations were defrayed from the Loomis Medical Research Fund of Yale University, and from a grant to one of us (A. L. P.) by the Committee on Scientific Research of the American Medical Association.

THE SYSTOLIC DISCHARGE AND THE PERICARDIAL VOLUME

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In a previous paper[1] we concluded from determinations of the oxygen pulse that the systolic discharge of the left ventricle of an athletic man during vigorous physical exercise with a pulse rate of 140 per minute cannot be less than 100 cc. of blood. We then pointed out also that if the heart obeys the principle of the "superimposability of the volume curve" the tidal volume of each ventricle at slow rates of beat in such a man must be 150 cc. or more. The tidal volume of the whole heart, that is, its change in size during a complete cardiac cycle, might then amount to 400 or even 500 cc. In persons of poor physique, judging by the relative amounts of oxygen consumed, it would probably be only a half or two-thirds as much. The purpose of the observations to be here reported was to determine whether the pericardial sack is large enough to allow the heart to make strokes of such magnitude.

Bohr[2] determined on a horse's heart the utmost volume to which the pericardial sack would allow the ventricles to be filled. From such measurements and from the amount of oxygen which a horse has been shown to consume during work he concluded that, even if the heart passed from the greatest distention which the pericardial sack would allow down to complete emptiness at each stroke, the systolic discharges would be insufficient to allow an oxygen pulse sufficient when multiplied by the heart rate to equal the animal's demonstrated oxygen consumption. Zuntz[3]

[1] This volume, p. 106.

[2] Skandinavisches Archiv für Physiologie, 1909, xxii, 221.

[3] Zuntz, Zeitschrift für klinische Medizin, 1912, lxxiv, nos. 3 and 4.

had the matter reinvestigated with the result that the maximal pericardial volume in the horse was found to be slightly more than the needed amount. There appear to be no measurements on record of the pericardial capacity in man suitable to a similar calculation.

The method by which our observations were made was as follows: At autopsy, after opening the thorax, a large hollow needle was inserted through the pericardial sack. A funnel was connected with the needle by a rubber tube, and water was poured in until no more would enter under a head of 20 cms. (It was found that only about 10 per cent more would enter under a head of 50 cms.) The pericardium was then opened, the veins and arteries ligated, and the heart removed from the body. The volume of blood in its chambers was determined either by catching it in a graduated cylinder, or else by immersing the heart before and again after the opening and emptying of its chambers in a vessel brim full of water and measuring the overflow. The sum of the pericardial and intracardial volumes expresses the total volume of blood which the heart would be allowed by the pericardial sack to contain at any instant during life. We shall suppose that one-third would be in each ventricle and one-sixth in each auricle. For the heart to make a stroke of such a volume would involve its passing from extreme dilatation to absolute emptiness. It is improbable that it ever does this or approaches it.

The data obtained were as follows:

Man, 48 years old. Height 160 cms. Well developed but emaciated. Cause of death, retro-peritoneal carcinoma. Pericardial capacity (i.e., the sum of the contents of the chambers and the volume of water that could be run into the pericardial sack) was 650 cc. One-third of this is 216 cc.

Man, 19 years old. Well developed. Height 175 cms. Death due to broncho-pneumonia. Heart normal. Pericardial capacity 700 cc. One-third of this is 233 cc.

Man, 33 years old. Height 178 cms. Weight 61 kilos. A muscular alcoholic. Died in delirium tremens. Pericardial capactiy 620 cc. One-third of this is 207 cc.

Woman, 55 years old. Height 165 cms. Cause of death, carcinoma of the gall bladder. Arterio-sclerosis. Heart valves thickened but competent. Pericardial volume 633 cc. One-third of this 211 cc.

Girl, 15 years old. Well developed. Weight 50 kilos. Cause of death, gas poisoning. Pericardial volume 430 cc. One-third of this is 143 cc.

Woman, 54 years old. Height 156 cms. Well nourished. Death from nephritis. Pericardial volume 350 cc. One-third of this is 117 cc.

Observations were also made upon six cadavers in the dissecting room. They had been embalmed with a fluid consisting of equal parts of alcohol, glycerine and carbolic acid, and the tissues were not considerably shrunken or hardened. One of them was a large and well developed man. Most of the others were originally of poor physique and had died of some wasting disease. The pericardial volumes were 572, 403, 348, 430, 310, 515.

Comparison of the pericardial volumes and maximum possible systolic discharges in the larger of these subjects with the oxygen pulses and calculated systolic discharges in subjects of good physique (e.g., Y. H. and M. A. M.) in our previous paper, and of the smaller pericardial volumes with the results obtained on subject of rather low oxygen consumption indicates that the pericardial sack in man is large enough to allow a systolic discharge considerably greater than there is any reason to suppose that the heart ever makes.

These observations were aided by a grant to one of us (A. L. P.) by the Committee on Scientific Research of the American Medical Association.

OVARIAN EXTIRPATION AND VASOMOTOR IRRITABILITY

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Although the relation between the ovaries and the sympathetic nervous system is considered at some length in gynecological literature the matter has received little attention at the hands of physiologists. This paper embodies the results secured in an investigation of the influence of ovarian extirpation upon vasomotor irritability. It is reported as the fourth of a series of studies[1] upon the relations between various endosecretory organs and the sympathetic nervous system.

Surgical extirpation of the ovaries of women of child-bearing age often results in a characteristic train of symptoms known as the artificial menopause. Various of these symptoms, as pointed out by Glaevicke[2] in 1889, indicate a condition of over excitability in the sympathetic system. This is manifested strikingly in the vasomotor instability which causes the characteristic "hot flashes" and dizziness. Excessive sweating, increased pulse rate and constipation which also occur supposedly have the same explanation. The manifestations appear about the fifth week after the operation. They typically occur intermittently ten or twelve times a day, gradually decreasing in frequency until they finally cease in about one and one-half years. The literature on this subject has recently been reviewed in a monograph by Schickele.[3]

[1] Hoskins and Wheelon: This Journal, 1914, xxxiv: 81, 172, 263.

[2] Gleavicke: Archiv für Gynakologie, 1889, xxxv: 1.

[3] Schickele: Innere Sekretion und Nervensystem (Band IV, Lewandowsky's Handbuch der Neurologie), p. 434. Berlin, 1913.

Adler[4] has noted an increased reaction to epinephrin in cases of ovarian deficiency or depression. A dose of 0.2 to 0.3 cc. of the drug in 1:1000 dilution which ordinarily produces little or no effect caused in Adler's patients increased pulse rate, a rise in temperature, polyuria and glycosuria. A Loewi reaction, i.e., mydriasis when epinephrin is dropped into the conjunctival sac, also was observed. These observations were regarded as showing the existence of "sympathicotonie." As evidence, however, they have little value. That augmented reactions to epinephrin indicate over-excitability or increased tonus in the sympathetic system is doubtful. In fact Elliott[5] has observed this condition as a characteristic result of sympathetic *degeneration*. We have had frequent opportunities to note that there is no necessary parallelism between the reactions to epinephrin and to nicotine which does give an index to the irritability of the sympathetics.[6] We have seen animals with a striking sensitiveness to nicotine in which the reactions to epinephrin were comparatively slight.

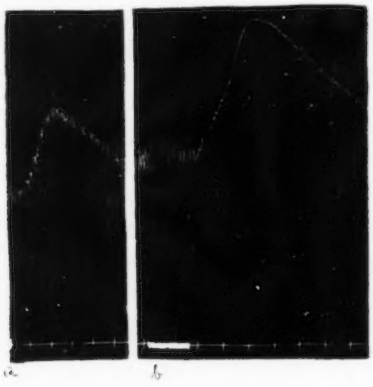
The fact that a small amount of surviving ovarian tissue, or, in some cases, ovarian grafts prevent the appearance of the artificial menopause indicates that a hormone is involved. This is supposedly a sympathetic depressant. As evidence in favor of this view Schickele[7] has reported that ovarian extracts have a strongly hypotensive influence upon blood pressure. Whether this, however, is due to any specific hormone is doubtful. Many tissue extracts, as is well known, have a similar influence.

Our experiments followed the general method of the preceding series. Blood pressure records were obtained using aseptic technique so that several records could be obtained from each animal. The reactions to standard quantities of nicotine gave an index of the irritability of the sympathetic nervous system proper and similarly the reactions to epinephrin indicated the condition of the peripheral vasomotor structures. The vasomotor system was selected as exemplifying the sympathetic system as a whole.[8]

[4] Adler: Archiv für Gynakologie, 1912, xcv: 349.
[5] Elliott: Journal of Physiology: 1905, xxxii: 401.
[6] Langley and Dickason: Journal of Physiology, 1890, xi, p. 297.
[7] Schickele: Biochemische Zeitschrift, 1912, xxxviii: 191.
[8] Hoskins and Wheelon: Loc. cit.

The degree of sympathetic irritability having been determined the animals were castrated and at intervals of approximately one and two months the irritability was again determined.

To remove the ovaries an incision was made in the median abdominal line. Through this the uterine cornu was palpated along the lateral body wall a few centimeters posterior to the kidney. The tube was grasped and drawn out through the incision and by traction upon it the ovary itself brought into view. Mass ligatures were placed about a centimeter distal to each pole and the tissues lying between, which included the gland and



Record of dog showing reaction to 0.5 cc. nicotine (1:2000 dilution), *a*, before, and *b*, 46 days after extirpation of the ovaries. Blood pressure from femoral artery. Time, 5 seconds.

the extremity of the tube were removed together. The operation was ordinarily performed with little hemorrhage or shock.

During the first month after the operation there was noted in some instances a decreased reaction to epinephrin and to nicotine, but in others some increase was observed. At this period no conclusions could be drawn. At the end of one and a half to two months, however, while the reaction to epinephrin was still indeterminate a very pronounced augmentation in the reactions to nicotine occurred. In one instance this augmentation was

more than 400 per cent, whereas in the animals of our normal series[9] the variability at different times was not anywhere nearly as great. One animal of the series failed to show any perceptible reaction to the castration. It may be conjectured that owing to old age or some other cause the ovaries of this dog were not functioning before the operation. As a matter of fact the worn condition of the teeth indicated that she was old. With this exception the results of the series were consistent and striking in degree. The average augmentation of irritability was some 200 per cent, about seven times as great as the average variability of the normal series. The accompanying figure shows the reaction to a standard dose of nicotine in one animal before operation and again 46 days later. More striking results could have been figured but this is about an average case. In this particular animal a depressed reaction had been observed at the end of 25 days. No significant variations in arterial pressure were observed. The fact that the reactions to epinephrin were not similarly increased indicates that the augmented irritability was neither in the sympathetic "receptive substance" nor in the vascular musculature but was in the sympathetic system proper.

Whether the augmented irritability would ultimately disappear in dogs as it does in the human species we have had no opportunity to observe.

There is a common supposition that the augmentation of irritability following parathyroid extirpation is due to perturbed calcium metabolism. Adler has investigated the effects of castration upon the calcium content of the blood. He found that this was materially decreased. He reported also that the coagulation time of the blood was increased. He ascribed both this increase and the sympathetic symptoms following surgical castration to a diminution of the calcium concentration in the blood (4). This theory affords a plausible explanation for the results of our experiments.

[9]Ibid: 81.

SUMMARY AND CONCLUSION

Ovarian extirpation in dogs results within six to eight weeks in a marked augmentation in the vasomotor reaction to a standard dose of nicotine. The reaction to epinephrin is not similarly increased. These results in conformity with clinical evidence indicate that the operation causes a heightened irritability in the sympathetic nervous system.

THE NATURE AND CAUSES OF THE RESPIRATORY PRESSURE VARIATIONS IN THE PULMONARY ARTERY[1]

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CONTENTS

I. THE NATURE OF THE PRESSURE CHANGES IN DIFFERENT TYPES OF NATURAL BREATHING

1. Previous work. In 1888 Knoll[2] showed that, in naturally breathing rabbits, the mean pressure in the pulmonary artery fell during inspiration and rose during expiration, thus confirm-

[1] The fourth of a series of papers on the pulmonary circulation, the previous papers of which were published in this journal, 1912, xxx, p. 233; 1914, xxxiii, p. 36; xxxiii, p. 382.

[2] Knoll: Sitzungsberichte der Akad. d. Wissenschaft in Wien, Math.-naturw. cl. 1888, part III, p. 208.

ing similar conclusions previously deduced by Talma[3] from studies of the right ventricular pressure. In 1904 Plumier[4] found that essentially the same variations of mean pressure occurred in the pulmonary artery of the dog when the cardiac rhythm was regular, but that the mean pressure rose in inspiration and fell in expiration when the heart accelerated during the phase of inspiration (cf. fig. I, *1*, *2*, *3*). In previous communications the writer[5] has also reported that, in the dog, where the respiratory cycle may be divided into active inspiration, passive expiration and an interval of respiratory quiet, both systolic and diastolic pressures fell during inspiration and rose during expiration. It was furthermore found that, if the heart was slowed during the expiratory phase, the systolic pressure was still increased while the diastolic pressure fell only when the slowing was very marked (fig. I, *4*, *5*). The mean pressure thus still fell during inspiration and rose during expiration. Moderate variations of the heart rate seemed, therefore, not to be the determining influence in the pressure variations in the pulmonary circulation.

Although investigators are thus agreed that the pulmonary arterial pressure falls during inspiration and rises during expiration, when the heart beat is regular, it is evident to anyone who has taken many records that so simple a relation is not always maintained. Plumier (l.c.) made the observation that this was true in the dog only when respiration was rapid, while, if the breathing was slow, so that a period of respiratory quiet intervened between inspiration and expiration, the mean pressure first fell and later rose during inspiration and first markedly increased and then for a longer interval decreased during expiration (fig. I, *2*). Such observations demand more detailed investigation since the type of "natural breathing" which predominates in the anaesthetized dog differs materially from that of man where inspiration and expiration succeed each other sixteen

[3] Talma: Arch. f. d. ges. Physiol., 1881, xxix, p. 311.

[4] Plumier: Arch. internat. d. physiol., 1904, i, 176.

[5] Wiggers: This journal, 1912, xxx, p. 248; 1914, xxxii, p. 8, N. B. In Table III of the first article the sixth and ninth column headings were by mistake interchanged with the heading of columns seven and ten. The former should read "expiration" and the latter "inspiration."

to eighteen times per minute without any intervening pause, the ratio of inspiration to expiration ranging from 1: 1.1 to 1: 2.7. Furthermore, the ratio of the heart beats to each respiration (H: R ratio) and the apportionment of the heart beats to the respiratory phases is entirely different. In man the H: R ratio

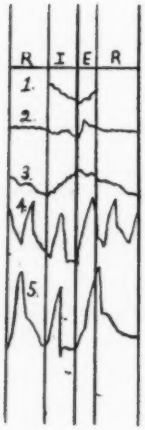

Fig. I

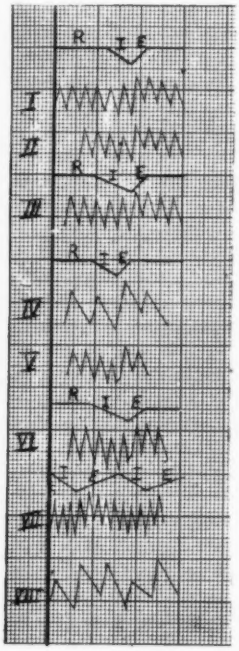

Fig. II

Fig. 1. Semi-schematic comparison of pressure changes in pulmonary artery during natural breathing as held by previous investigators. *1*, Mean pressure curve during rapid breathing (Knoll, Plumier). *2*, Same during slower breathing (Plumier). *3*, Same during slow breathing with respiratory variations of cardiac rhythm present (Plumier). *4*, Systolic and diastolic pressures during slow breathing, heart regular (Wiggers). *5*, Same, heart slowed in expiration and accelerated during inspiration (Wiggers). *I* = inspiration, *E* = expiration, *R* = respiratory rest.

Fig. II. Plots from optical records showing the effect of different types of normal breathing and different H : R ratios on the systolic and diastolic pressures in the pulmonary artery. Lettering same as in figure I.

is approximately 4.5: 1, while in animals it may be extremely variable (3: 1 to 15: 1). Reserve and caution must therefore be exercised in translating the pressure changes found in the dog to man.

2. Results of this research. In investigating the influence of different types of breathing as well as different H: R ratios on the pressure variations in the pulmonary artery *the mercury manometer cannot be used* not only because it fails to follow the pressure changes rapidly enough, but also because its own period (1 per second) is so low that a resonance effect is often produced. The Hürthle manometer (straight spring pattern), when so employed that its vibration period is kept as low as possible, is serviceable provided neither the quantitative variations nor the finer details are demanded. However, owing to the fact that it is

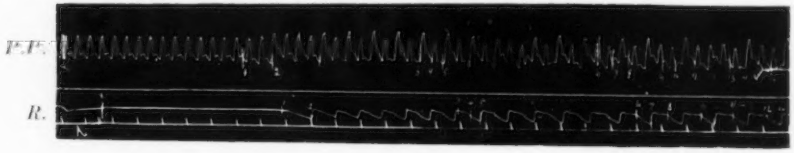

Fig. III. Effect of apnea vagi and different types of breathing on pulmonary arterial pressures. *P.P.*, pulmonary arterial pressure recorded by the Hürthle spring manometer.

not feasible to make the ratio of the recorded curve to the actual pressure changes greater than 1: 5, it may happen that an actual deviation less than 5 mm. will be entirely obscured by the friction of the lever. For this reason, the records of pulmonary pressure changes obtained several years ago during different forms of breathing, have recently been reinvestigated and corroborated by tracings with optical manometers. The nature of these records is shown in figure V. Owing to the reduction in size necessary for publication, many of these records lose a great deal of their illustrative value, hence the chief details of selected experiments have been summarized in the plots of figure II, while several of the older Hürthle records, are introduced as figures III and IV on account of their compact nature.

A study of these records and plots makes evident the following conclusions:

1. During an extended period of apnea both systolic and diastolic pressures are equal (figure III).

2. When the phase of expiration is separated from succeeding inspiration by a period of respiratory rest and the acts of inspiration and expiration begin exactly at the systolic upstroke, then, (a) inspiration reduces the systolic and diastolic pressures of the first and often the second wave, but *occasionally* the second and *generally* the third wave show an increase of systolic pressure; (b) the act of expiration always elevates both systolic and diastolic pressures above the last inspiratory pressures and (c) during the phase of expiratory rest both pressures progressively fall until the apnea level is reached (see plots I, II, III and IV of figures II and III).

3. When inspiration begins during diastole, the diastolic pressure is immediately decreased and the systolic pressure of the next wave materially reduced so that the pulse pressure is smaller. When expiration starts during diastole, the diastolic pressure is immediately augmented and apparently offers a support to the next wave, which reaches a high summit (plot V, VI of figure II and waves 6, 7, 8, 9, 10 and 11 of figure III).

4. When inspiration and expiration gradually merge into each other both systolic and diastolic pressures fall for two beats or so in inspiration but if more beats occur the systolic pressure rises again. During expiration both pressures rise greatly during its early portion, but subsequently fall again towards the end of expiration (plots VII, VIII of figure II, also figure IV).

Summary. It is evident that the occurrence of a pause after a rapid expiration causes pressure variations that are no different than when expiration and inspiration follow each other immediately. In both cases the pressure first rises and later falls; the extent of the fall depending entirely on the number of heart beats occurring before the next inspiration. Whether the systolic pressures merely fall in inspiration or subsequently rise again depends on the number of heart beats during the phase of inspiration. If not more than two beats occur, as is the rule in man,

the pressures always fall; whereas, if more beats occur, the systolic pressure, as a rule, increases again.

II. THE CAUSES OF THE PRESSURE VARIATIONS

Since the variations of pulmonary arterial pressure occur when cardiac rhythm is regular and the effective right auricular pres-

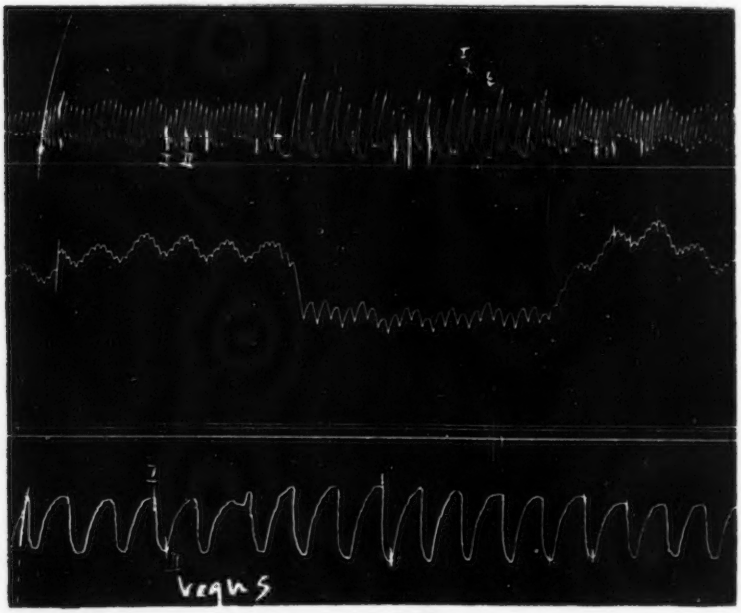

Fig. IV. Effect of breathing in which no expiratory pause exists when H : R ratio is great and small (vagus stimulation) *C.P.*, mean carotid pressure; *S*, stimulation, letters otherwise same as before.

sure is at or above the level found in unanaesthetized animals, it is logical to assume that similar changes take place in the pulmonary circuit of unoperated animals, and since these changes are related to inspiration and expiration they are probably due to the influence of respiratory movements.

No explanation of these changes may be regarded as satisfactory which fails to account for the detailed changes in systolic and diastolic pressure. Briefly recounted, four questions must be definitely considered. (1) Why do the systolic and diastolic pressures first fall during the act of inspiration? (2) Why, when more than two pulse beats occur during inspiration, does the systolic pressure increase again? (3) Why do both systolic and diastolic pressures increase during the act of expiration and (4) Why do both systolic and diastolic pressures gradually fall again during the expiratory pause or the end of a prolonged act of expiration.

Two causes, acting separately or together, may be responsible for these variations, namely, a change in the systolic discharge of the right ventricle or a variation in the total pulmonary vascular resistance.

A. The output of the heart as a factor

1. Previous work. (a) *Return of venous blood during inspiration.* It is generally recognized that the arterial pressure, hence presumably the cardiac output, are materially affected when the return of the blood to the right heart is modified by compressing the abdomen or ligating the inferior vena cava. It is not surprising, therefore, that considerable attention should have been directed to the effect of respiratory movements on the blood flow to the thorax. The observations of Haller[6] in 1760, that the neck veins swelled during expiration and collapsed during inspiration, have been abundantly confirmed and given objective demonstration through strohmuhr experiments, and venous pressure measurements (Burton Opitz[7]). It does not admit of question, therefore, than an increased flow from the neck veins into the thorax occurs during inspiration.

As to the precise cause of this augmented inflow during inspiration, opinions differ slightly. Many physiologists have followed the teaching of Barry[8] that the greater difference between

[6] Haller: Quoted by Tigerstedt, Ergebnisse der Physiology, II_2, p. 549.
[7] Burton Opitz: Amer. Journ. Physiol., 1902, vii, p. 443.
[8] Barry: Quoted in Schafer's Text-book of Physiology, 1900, ii, p. 122.

the intra- and extrathoracic pressures existing during inspiration supplies a continuous suction force. Others hold with de Jager[9] who, in 1879, stated that the inspiratory negative pressure increased the caliber of the large veins within the thorax. Upon this assumption an increased flow would be possible only during the act of inspiration and not during any permanent variation of pressure. Evidence has also been presented to support the idea that the inspiratory descent of the diaphragm compressed the abdominal veins and so converted the chest and abdomen into a combined force and suction pump. Kuhn[10] in 1875 showed that the respiratory waves of arterial pressure persisted in the carotid after opening the chests of animals and Schweinburg,[11] in 1881, found a reduction of the carotid pressure variations when the abdomen was opened or the phrenic nerves sectioned in dogs. de Jager[12] showed that this abdominal effect was really exerted on the abdominal veins and not directly on the aorta, for, if the latter were the case, the femoral and carotid pressures should vary in opposite directions which they did not do.

Not all investigators, however, share the belief that the increased abdominal pressure is normally concerned in increasing the flow to the right heart. Thus Lewis[13] found that an intra-abdominal pressure far greater than normal must be applied in order to affect the systemic pressure variations in the cat and Eppinger and Hofbauer[14] point out that, during the inspiratory descent of the diaphragm, the lumen of the inferior vena cava is lessened, so that the influx of blood to the thorax is impeded. Should this prove correct, the augmented inflow from the neck veins might merely counterbalance the decreased flow through the inferior vena cava. It remains doubtful, therefore, whether it has been demonstrated that a greater volume of blood is supplied to the heart during inspiration.

[9] de Jager: Arch f. d. ges. Physiol., xxxiii, p. 17.
[10] Kuhn: Quoted by de Jager (l. c., p. 21).
[11] Schweinburg: Arch. Physiol., 1881, p. 475.
[12] de Jager: Journ. of Physiol., 1886, vii, p. 202.
[13] Lewis: Journ. Physiol., 1908, xxxvii, p. 240.
[14] Eppinger and Hofbauer: Zeitschr. für klin. Med., 1911, lxxii, p. 154.

(b) *The systolic output during inspiration and expiration.* Even if the assumption that a greater influx of blood to the thorax occurs during inspiration, is granted, it does not carry with it the a priori deduction that a larger volume of blood is necessarily ejected by each beat of the right ventricle. Experimental evidence, in fact, has been interpreted otherwise. Tigerstedt[15] and others have found that the mean pressure within the right ventricle falls during inspiration, evidence at one time regarded by Tigerstedt as indicating a decreased output. The writer[16] also pointed out that, when a cardiometer was applied to the heart and the chest subsequently repaired, the strokes during inspiration were less than during expiration, apparently indicating that the output decreased during inspiration. Such experiments, however, may no longer be regarded as carried on under normal conditions, for, as Henderson and Barringer[17] pointed out, in commenting upon certain experiments of Lewis, the changing intrathoracic pressure plays upon the veins and auricles but not upon the ventricles and so reduces the effective pressure.

The recent work of Henderson and Barringer has lifted the entire question of ventricular output to a more approachable level. These investigators point out that, in the open chest, the filling of the ventricle and its output are determined by the auricular pressure and that the quantity of blood in the auricles affects their filling only in so far as it modifies the filling pressure. Within the closed chest the filling of the ventricle is determined, not by the actual auricular pressure, but by the effective auricular pressure, i.e., the difference between intraauricular and intrathoracic pressures. Applying their conception to the influence of respiration on the blood stream, these writers maintain (l.c.) that when the effective auricular pressure exceeds 50 mm. it has passed a "critical" pressure point at which the output is maximal so that any further increase in pressure produces no additional discharge. Now, since these investigators believe that

[15] Tigerstedt: Skan. Arch. f. Physiol., 1903, **xiv** p. 259.
[16] Wiggers: Arch. Inter. Med., 1910, vi, p. 5.
[17] Henderson and Barringer: Amer. Journ. Physiol., 1913, xxii, p. 402.

the effective pressure is always above the critical level, they assert that the acts of respiration must be incapable of modifying the cardiac output. They go further and insist that, as a matter of fact, no variation of the effective venous pressure is conceivable, the pressure falling in the jugular vein by an amount exactly counterbalancing the drop in the intrathoracic pressure. Thus, on two grounds, they insist on the impossibility of the output being affected by the acts of respiration.

If the mechanism of the right heart can be put on so simple a basis, it materially simplifies our analysis of the pulmonary pressure variations. Accordingly, the writer[18] recently sought to verify the position of Henderson and Barringer (l.c.). It was found, however, that while the beats of the heart became approximately superimposable at an effective pressure in the proximity of 50 mm. of water, it by no means followed that no further increase in output was possible when the auricular pressure exceeded this level. Furthermore, it was found that the effective pressure in the right auricle increased slightly during inspiration an observation which the writer at first interpreted to mean that the greater influx of blood during inspiration raised the hydrostatic pressure by distending the veins.

At the time this report was made the writer was unaware of a paper recently issued by Piper,[19] who found by optical methods no difference between the effective venous pressure during inspiration and expiration in the cat, thus upholding the views of Henderson and Barringer. Without entering into details to be subsequently reported, the statement may be made that the writer has confirmed his previous results by optical methods and believes Piper's conclusions to be influenced by technical points apparently not recognized by him.

Critically sifted, there is no evidence available that, during inspiration, either the blood flow to the heart or the effective venous pressure is so altered as to cause a *decreased output* during inspiration, *yet such an assumption would be necessary to explain the fall of pressure which is the chief variation during this respi-*

[18] Wiggers: This journal, 1914, xxxiii, p. 13.

[19] Piper: Arch. f. Physiol., 1913, p. 396.

ratory phase. On the other hand, all the evidence indicates that the venous pressure variations are favorable for an increased output, which may perhaps account for the fact that the systolic pressure rises when more than two beats occur during inspiration.

B. Variations in the total pulmonary arterial resistance

1. Previous work. (a) *The effect of lung inflation on the intra-pulmonic vessels.*

pulmonic vessels. The influence of inspiration and expiration on the caliber of the pulmonary vessels has been studied in several different ways. Perfusion of the lung vessels has been a favorite method of investigating the influence of inflation produced by both positive pressure and negative suction. This work, carefully reviewed by Tigerstedt,[20] shows that most investigators found an increased flow through the lungs during inspiration. Clamping the roots of the lung at the end of expiration and inspiration has been found unsatisfactory,[21] for, aside from the fact that the results are discordant, the method does not distinguish variations in blood content due to an altered output from those due to a change in the vessels themselves. Histological examination of collapsed and inflated lungs are reported by Poisenille to show that the lung capillaries are longer and narrower, findings recently corroborated by Cloetta.[22] Continuing his investigations Cloetta[23] subsequently pointed out that two opposite forces act upon the intra-pulmonary vessels when the lungs expand. (1) The radial traction of the expanding alveoli tends to enlarge the vessels between them but this force is soon converted into an actual compression when the alveoli acquire the polygonal shape of inspiration. (2) When the lungs enlarge, a linear traction is exerted which lengthens the vessels and thereby reduces their caliber. The conclusion is reached from these histological studies that the forces causing an increased

[20] Tigerstedt: Ergebnisse der Physiologie, II_2, 1903, 551.
[21] For references see Cloetta: Arch. f. Exp. Path. u. Pharm. 1911, lxvi, 414.
[22] Cloetta: Arch. f. exp. Path. u. Pharm., lxvi, p. 57.
[23] Cloetta: Arch. f. Exp. Path. u. Pharm., lxx, 1912, p. 407.

resistance during lung expansion always more than counterbalance the dilating influence.

Cloetta (l.c.) also substantiated these deductions by enclosing a lung within a plethysmograph. When the lungs were inflated by a negative pressure, the lung pulsations from the plethysmograph decreased, the systemic pressure fell and the pulmonary arterial pressure rose. These observations were interpreted to show that when the lungs were inflated, the resistance within the pulmonary system increased. Upon such an hypothesis, however, it would be difficult to explain the fall of pulmonary arterial pressure during natural inspiration. Cloetta, however, carried his work still farther and showed that, if the lungs within the plethysmograph were only partially inflated, both pulmonary and systemic arterial pressures fell. The former fact is interpreted as indicating that, when the lungs are only partially inflated, the dilating influence of radial traction becomes supreme and the lungs are in the most favorable condition for a larger blood flow. Since these changes were obtained only when very small negative pressures were applied about the lungs (1 to 3 cm. water), it remains questionable whether they are entirely responsible for the fall of pressure in the pulmonary vessels during natural inspiration.

(b) *The effect of negative pressure on the extrapulmonary vessels.* Although the evidence thus presented apparently shows that, except during very slight inflation, the resistance of the vessels within the lung increases with lung expansion, it should be borne in mind that the entire resistance is not determined by the size of the smaller intrapulmonary vessels alone. "The diminution in the diameter of a tube at a small part of its length," states Lewis,[24] "allows no estimate of the resistance in the remaining portion."

de Jager[25] has supplied interesting evidence as to the effect of negative pressures on the extrapulmonary vessels. He showed that, when both the pulmonary artery and vein were submitted

[24] Lewis: Journ. of Physiol., 1908, xxxvii, p. 229.

[25] de Jager: Arch. f. d. ges. Physiol., 1879, xx, p. 491.

to the same negative pressure, the vein which was thinner walled dilated while the arterial diameter decreased. Apparently this occurred because the dilation of the vein lessened the venous pressure which, by diminishing the "vis a fronte," increased the flow from artery to vein and consequently reduced the pressure and caliber of the artery. According to this observation, which has, to the writer's knowledge, never been repeated, the caliber of the pulmonary vessels depends partly on external and partly on internal pressures of the arteries. It is conceivable that a similar decrease in the "vis a fronte" may be brought about by a dilation of the left auricle or, even as Lewis (l.c.) suggests, by an increased filling of the left ventricle due to a more negative pericardial pressure.

It is evident that a change in the *total resistance* within the pulmonary circuit *is the resultant* of (a) a changing capacity of the extra and intrapulmonary arteries and branches, (b)the changing resistance of the smaller arterioles and capillaries and (c) the changing venous and left auricular pressures. Neither the *resultant change* nor the share it plays in determining the pressure variations in the pulmonary artery have been determined.

Some authors have gone so far as to deny the probability that variations in the caliber of the pulmonary vessels play any part in the production of the respiratory pressure changes. Since the total resistance in the pulmonary circuit is without question very low and the experiments of Lichtheim and Tigerstedt[26] have indicated that a considerable increase in resistance caused by ligating the pulmonary vessels was without effect on the arterial pressure and failed to increase the maximal right ventricular pressure, Tigerstedt believed that the comparatively slight changes of resistance such as are possible during natural breathing must be entirely without effect on the flow through the lung. The writer, on the contrary, has recently shown that the ligation of a single branch of the pulmonary system causes a modification of the pressure curve in the right ventricle, so that Tigerstedt's argument looses its force. Furthermore, the obser-

[26] Tigerstedt: Skan. Arch. f. Physiol., xiv, p. 231, 1907.

vations of Knoll[27] and the writer[28] that the pulmonary arterial pressure falls during inspiration even when the heart is stopped favors the idea that a direct effect on the vessels causes the fall of arterial pressure.

C. Experimental results of this investigation

1. The intra-ventricular pressure curve as a criterion. When the probability is great that many forces are concerned in the production of a reaction, it is often desirable not to separate the problem and study the detailed forces at work, but, in order to obtain the correct effect of their interaction, to study them by a method capable of differentiating between their efforts. In applying this principle to the pulmonary circulation, the attempt was made to determine to what extent variations in the systolic discharge account for the pressure changes. The changes not so accounted for are then necessarily due to variations in the total pulmonary resistance. It has not been a simple matter to determine correctly the consecutive systolic discharges of the right ventricle. The introduction into the pulmonary artery of a strohmuhr sufficient in size and adequate in quality, as well as its operation within the closed chest has so far not proven feasible. The application of a cardiometer to the ventricles is objectionable, not only because it is difficult to maintain a correct placement within the closed chest but also because it has not been proven that the discharges of the two ventricles are equal in the same beats. Furthermore, the influence of a varying negative pressure is thus removed from the ventricle and retained around the auricles and so unnatural conditions are produced.

A preliminary study of the pressure curve within the right ventricle by manometers capable of accurately reproducing the details of the pressure variations gave promise of a method by which the subject could be approached with a minimal inter-

[27] Knoll: Sitz-Ber. d. Akad. d. Wiss. in Wien Math.-naturw. cl., 1888, xcvii, part III, p. 207.

[28] Wiggers: Amer. Journ. Physiol., xxxiv, 1914.

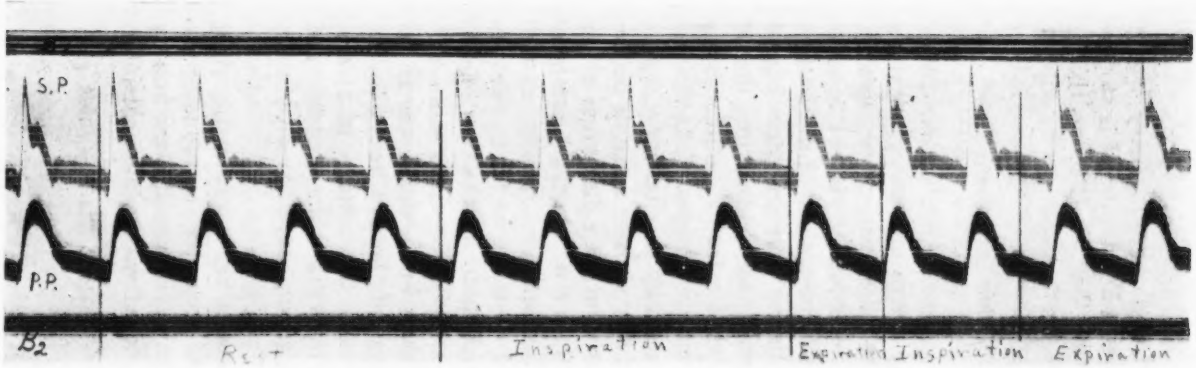

Fig. V. Optical tracings of pulmonary arterial (*P.P.*) and systemic (*S.P.*) pressure variations in typical experiment. Showing the effect of expiratory rest, an inspiration with four heart beats, an expiration with one beat and an inspiration with only two heart beats. B_1 base line for systemic pressure, *S.P.*: B_2 base line for pulmonary arterial pressure *P.P.*

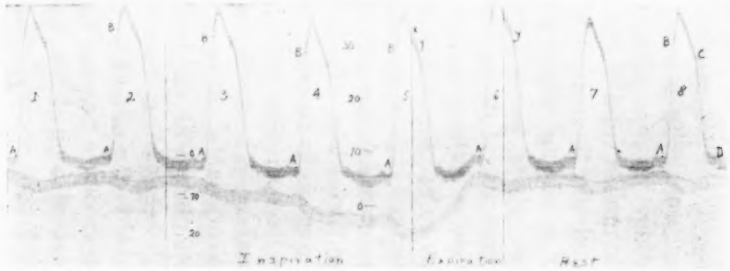

Fig. VI. Right intraventricular (upper) and intrathoracic pressure (lower tracing) during natural breathing. Figures show calibration expressed in mm. of mercury. Letters referred to in text.

ference of the circulation. In utilizing the intraventricular pressure curve as a criterion it is necessary to have definitely in mind in what ways it can give information as to changes in cardiac output. According to the studies of Henderson and his coworkers[29] the heart's systolic discharge may be modified by (1) a change in the auricular filling pressure and (2) by a change in the tonus and relaxation. To these may be added a third, namely, an inherent change in the contraction rate of the ventricle.

It may be briefly recalled that that portion of the intraventricular pressure curve written during systole can by analysis be divided into two periods (figure VI) an isometric period *A B* during which the valves remain closed and the tension increases and an ejection period *B C* divided again into an ascending limb and a descending limb. The variations in the filling pressure may be accurately estimated by determining the initial tension within the ventricle (at *A*) in calibrated records. In doing so allowance must obviously be made for the variation of the intrathoracic pressures. Variations in the rapidity of the ventricular contraction, whether due to an inherent change in the rate of contraction or secondary to an altered initial pressure are indicated by the gradient of the isometric upstroke. It is quite conceivable, however, that with the same initial tension and upstroke the output might still vary as a result of an altered tonus but this would be evidenced by a slower relaxation after closure of the semilunar valves (i. e., the slope *C D*).

2. Procedure and results. The intraventricular pressure was recorded by introducing the long sound of an optical manometer, recently described[30] through the jugular vein isolated as far down as possible. The effort was made to place the end of the sound, containing two lateral openings just within the ventricular cavity and only those experiments where its proper placement was verified by subsequent opening of the thorax were accepted in this analysis. The manometer was calibrated in relation to a perm-

[29] Henderson and Barringer: Amer. Journ. Physiol., 1909, xxiii, p. 345; 1913, xxxi, p. 361.

[30] Wiggers: This journal, 1914, xxxiii, p. 385.

anently recorded base line as described in the previous paper. The intrathoracic pressure variations were recorded through a thoracic trocar inserted toward the center of the thorax and connected by air transmission with a calibrated Frank's segment capsule.

An analysis of many records such as are shown in figure VI as well as those recorded on more rapidly moving paper show that the systolic summit as in the pulmonary artery falls during natural inspiration in the first two beats but rises again if more beats occur during that phase of respiration. The conditions are therefore comparable to the experiments in which the pulmonary pressures were recorded.

The initial tension within the ventricle decreases (measurement at dots labeled A) but the fall is not quite as great as the pressure within the thorax thus making what may be designated the *effective initial tension* a trifle greater, an observation supporting the increase in the effective auricular pressure previously reported (see table I).

TABLE I

	WAVE NUMBER							
	1	2	3	4	5	6	7	8
Intraventricular pressure...	+9.6	+9.6	+9.0	+7.6	+6.0	+9.6	+9.5	+9.6
Intrathoracic pressure.....	−4.0	−4.0	−5.5	−9.4	−13.9	−4.0	−4.0	−3.3
Effective pressure.....	13.6	13.6	14.5	17.0	19.9	13.6	13.5	12.9

Figures translated to millimeters of mercury.

Confining our analysis to the first two waves of inspiration (in waves 3, 4), it is found that the gradient of the isometric period usually shows not the slightest deviation. In only two experiments, regarded as technically less reliable, the slope became very slightly steeper. The gradient of the upstroke was determined in all cases by projecting the slope to cross-section paper and then measuring the angle of its ascent with a protractor. Furthermore, due to the optical principles involved, the width of the band of light becomes narrower as the steepness increases and wider when

it decreases, thus rendering changes readily visible. The relaxation period shows no alteration in slope. *Hence a decreased output was not the cause of the lower summit.* The isometric period terminates at a lower level, *B*, after which the pressure during the ejection period rises more rapidly, reaches a sharper peak and then rapidly falls until the beginning of the relaxation period. Since similar changes were previously obtained[31] when the lungs were artificially inflated in the open chest, and this type of ejection period is obtained when the resistance is otherwise decreased, the conclusion seems obvious that the decrease in pressure is due to a decreased *total resistance* in the pulmonary circuit.

In the third wave of inspiration (i.e., wave 5) in which the systolic summit becomes higher, the effective pressure is greater than before, and the isometric incline is steeper, hence the output is probably increased for the relaxation of the previous beat apparently remained unaltered. This probably accounts for the higher summit of the ejection period. After the summit the curve falls downward acutely. In the curve shown in figure VI, expiration begins at *x* and causes the slope during systole to become more horizontal. This indicates that probably the resistance is increased by expiration. The relaxation curve beginning at y shows no altered rate of relaxation. In the following beat of expiration (i.e., wave 6) the initial pressure has slightly decreased yet the gradient of the isometric period becomes steeper and terminates at a higher level, indicating that in addition to the increased total resistance the output is also increased. The ejection curve assumes a more rounded contour characteristic of a higher resistance.

3. Application of results to the interpretation of pulmonary arterial pressure variations. 1. The systolic and diastolic pressure in the pulmonary artery usually falls during the first two inspiratory beats. The right ventricular curves during these beats are superimposable with those of expiratory rest as far as the gradient of the isometric rise and the relaxation are concerned.

[31] See this journal, 1914, xxxiii, p. 392.

The effective initial pressure is slightly augmented. The pulmonary arterial pressure changes are therefore not due to a decreased output but, to judge from the contour of the ejection curve, are due to a decrease in the total pulmonary arterial resistance.

2. The systolic pressure of the third inspiratory wave is increased while the diastolic pressure remains low. Since the intraventricular pressure curve gives evidence of a greater effective initial tension and a steeper rise of the isometric period, the increase in systolic output so indicated probably accounts for the higher pulmonary systolic pressure during this beat.

3. During the act of expiration both diastolic and systolic pressures are increased, the diastolic pressure often during the period that no blood is ejected. Since a change in the shape of the ejection period occurs when expiration begins during ventricular systole, the increase in the total pulmonary resistance is no doubt partly responsible for the pressure increase but inasmuch as the gradient of the isometric upstroke is also increased, an augmented ventricular discharge is also probable.

Further experiments have already been instituted to determine the causes of the variations of output during the acts of respiration and to analyze more in detail the factors involved in the modification of the total pulmonary arterial resistance.

THE CLOTTING OF BLOOD AS SEEN WITH THE ULTRAMICROSCOPE

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Several observers have applied the ultramicroscope to the study of the process of clotting. According to Mayer,[1] whose description of the process is confirmed in the main by Cesana,[2] what occurs is first the appearance of minute granules or particles in what was before (Mayer) an optically empty field. These granules then agglutinate to form rows or threads in which the constituent particles are still visible, or in the case of more massive coagulation, such as occurs in normal clotting, the granules agglutinate into masses from which later fibers are formed and eventually a sponge work or honeycombed structure. In a recent paper by Stübel[3] a very different description is given. This author used the dark field illuminating method (parabaloid or cardioid condenser) and was able to show that, in most cases at least, the fibrin is deposited in the form of definite needles which give rise to a meshwork throughout the liquid. The formation of these needles resembles the process of crystallisation. In bird's blood as a rule, and in frog's blood always, according to Stübel the process differs from that seen in mammalian blood in that the fibrin appears as a network instead of as isolated needles.

At the time that Stübel's paper appeared the author was preparing to follow the process of clotting under the ultramicro-

[1] Mayer: La coagulation du plasma sanguin. Comptes rendus de la société de biologie. 1907, lxiii, 658.

[2] Cesana: Ricerche ultramicroscopiche sulla coagulazione del plasma di sangue. Archivio di Fisiologia. 1908, v, 180.

[3] Stübel: Ultramikroskopiche Studien über Blutgerinnung und Thrombocyten. Pfüger's Archiv. 1914, clvi, 361.

scope with the intention of using pure solutions of fibrinogen and thrombin. The results attained are so decisive, in some points, as to merit a brief description. The apparatus used in the work consisted of the slit ultramicroscope of Siedentopf and Zsigmondy for liquid colloids. Illumination was obtained from sunlight reflected by a heliostat. Most of the observations and all of the photographs were made with the water-immersion objective D and ocular 2. The material used for observation consisted of the oxalated blood-plasma from various animals (man, dog, cat, horse, terrapin) which had been centrifugalized at high speed for half an hour, so as to give a corpuscle-free liquid. This plasma was made to clot, while under observation with the ultramicroscope, by the addition of a suitable amount of an aqueous solution of thrombin. The thrombin was made by a method previously described.[4] Its solutions are water-clear. In addition to the clotting of the oxalated plasmas a great many observations were made on mixtures of fibrinogen solutions and thrombin. In these cases the fibrinogen was prepared from plasma by the successive precipitations with half-saturation of sodium chloride. The last precipitate, after centrifugalizing and washing, was dissolved in a 0.9 per cent solution of sodium chloride to which was added a trace of a dilute solution (0.5 per cent) of sodium bicarbonate. The mixtures of plasma and thrombin or of fibrinogen and thrombin were poured into the funnel attached to the cell (Biltz form of apparatus) as soon as made and then immediately brought into the cell for observation.

RESULTS

When the amount of thrombin is adequate to produce a firm clot within a few minutes the process of clotting proceeds in substantially the same way in all plasmas observed. The end-result is the formation of a meshwork of beautiful needles, which stand out brilliantly in the field as rigid acicular structures. The process of clotting, as Stübel says, proceeds after the manner of crystal formation. There is no indication of the existence of

[4] Howell: Rapid method of preparing thrombin. American Journal of Physiology. 1913, xxxii, 264.

fibers or of a network. The character of the meshwork of needles is shown sufficiently well in the illustrations[5] (figs. 1, 2, 3), so that a further description is unnecessary. The matter of greatest interest was to attempt to follow the actual process of formation of these needles. With the slit-ultramicroscope this is possible up to a certain point. When the proper proportion of thrombin is used the process takes place uniformly throughout the field of observation. Bright specks appear first as short rods, which exhibit a genuine saltatory movement, jumping abruptly into and out of focus, and quickly fusing to form longer rods and needles. The process shows most beautifully perhaps with solutions of fibrinogen and thrombin, but when the formation of crystals occurs quickly it is difficult to follow the process in detail. I have examined the solutions of thrombin, fibrinogen, and plasma, before mixing, and also mixtures made with varying proportions of thrombin. The aqueous solutions of thrombin employed, when examined under the ultramicroscope showed scattered particles that exhibited Brownian movement as well as movement of translation through the field. The field itself was nearly dark showing only a faint indication of a cone even with the intense illumination of a bright sun. The solutions of fibrinogen and also the plasmas showed a number of particles in active Brownian movement, and in addition a strongly luminous cone in which individual particles could not be distinguished. According to my observations it is in this background of particles beyond the resolving power of the ultramicroscope that the needles are formed. In some cases (fibrinogen from terrapin's plasma) I have seen this uniform luminous field when thrombin was added, take on a granular or particulate appearance, the particles subsequently adhering in strings or threads as described by Mayer. When fibrinogen from the mammal was used and an adequate amount of thrombin, the bright bacillus-like rods that first appear are born in this field, and when the process is over and the meshwork of needles is formed the luminous background has disappeared. It would seem therefore that under the influence of the thrombin there is first an aggregation of the

[5] I am greatly indebted to Dr. Daniel Davis, assistant in physiology, for making the photographs used to illustrate this paper.

invisible particles (amicrons) to visible particles and then the further consolidation of these particles into the rigid looking needles. The active jumping movements of the short rods when first formed especially in the fibrinogen solutions, before they fuse into the longer needles, strongly suggest an influence of electrical attraction and repulsion. When the quantity of thrombin added is not sufficient to cause prompt clotting, the process of production of the needles is less striking. Individual needles are formed that float into and out of the cone of light, and often they appear slightly bent or curved. Eventually in such cases they form loose clusters or a loose meshwork, between which are seen many dancing particles. So far as my examination has gone all the plasmas used exhibit this needle formation, or deposition of fibrin crystals, but in the plasma of the horse and of the terrapin the needles are smaller and finer than in the plasmas of the dog or cat or in human plasma. So also in the fibrinogen made from the horse's plasma the needle formation is less striking than in that from the other mammals used (see fig. 5), while in the fibrinogen prepared from the terrapin's plasma the formation of the acicular crystals is still less complete. At the end of the process one sees a meshwork of threads or rods of varying length and size, exhibiting a beaded appearance as though composed of particles incompletely fused.

CONDITIONS MODIFYING THE FORMATION OF THE FIBRIN NEEDLES

Changes in the formation of the needles have been observed under the following conditions. (1) In cat's plasma made to clot by the addition of thrombin the size of the crystals varied with the rapidity of clotting. A large amount of thrombin caused very rapid clotting with the production of small although very distinct needles, while with a small amount of thrombin the clotting was slow and the needles were relatively very large, as seen in figure 4. (2) With very dilute solutions of fibrinogen and of thrombin such as give a loose clot, the fibrin needles were well formed but adhered in loose more or less separate clumps instead of forming a solid uniform meshwork. (3) In mixtures of fibrinogen and thrombin in which the amount of the latter

was insufficient to give a firm clot it was observed in several cases that the fusion of the particles might show varying degrees of completeness. In some cases the particles aggregated in smaller or larger clumps or heaps in which the separate particles were distinctly visible. In such cases the smaller clumps showed Brownian movements, and the separate particles in the clumps might exhibit independent movements. On standing the clumps may again disintegrate into particles or aggregations of particles. In other cases in which the thrombin was insufficient in amount the particles adhered to form short rods or longer beaded threads, giving the appearance of an abortive attempt at the production of needles. (4) Partially denatured fibrinogen gives an imperfect formation of fibrin needles under the influence of thrombin. This effect was observed especially with specimens of dried plasma. The author has employed dried plasma in experiments upon the quantitative estimation of antithrombin in the blood. This plasma is prepared by oxalating blood, centrifugalizing to get a clear plasma and then dializing against salt solution in tubes of collodion to remove the excess of oxalate. The plasma thus prepared may be dried in small quantities and used subsequently for coagulation experiments after redissolving in solutions of sodium chloride 0.9 per cent. These solutions give a good clot when thrombin is added, but under the ultramicroscope it was found that there was never a formation of typical fibrin needles. The meshwork was composed of short rods or strings or longer threads in which for the most part the separate particles could be distinguished.

SUMMARY

The paper gives a description of the phenomena observed under the ultramicroscope when solutions of thrombin are added to oxalated blood-plasma or to solutions of fibrinogen. The essential point is that the fibrin formed is deposited not as a network but as separate well-formed needles of crystalline appearance which are massed to produce a mesh. Under certain conditions the process is incomplete, giving rise to the production of threads or rods of different lengths in place of the needles.

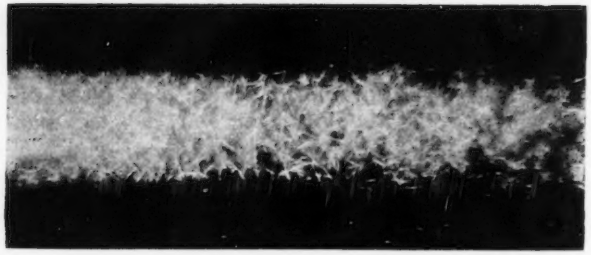

FIG. 1

FIG. 2

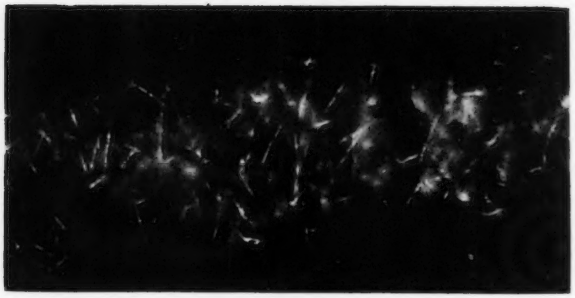

FIG. 3

Figs. 1, 2, and 3. Figure 1, oxalated plasma of human blood clotted with thrombin. Photographed under low magnification (257) to show a portion of the cone and the nature of the mesh formed by the fibrin needles. Figure 2, oxalated plasma of human blood clotted with thrombin, magnification 512, to show the details of the needles. Figure 3, Fibrinogen solution made from cat's plasma and clotted with thrombin, magnification 512.

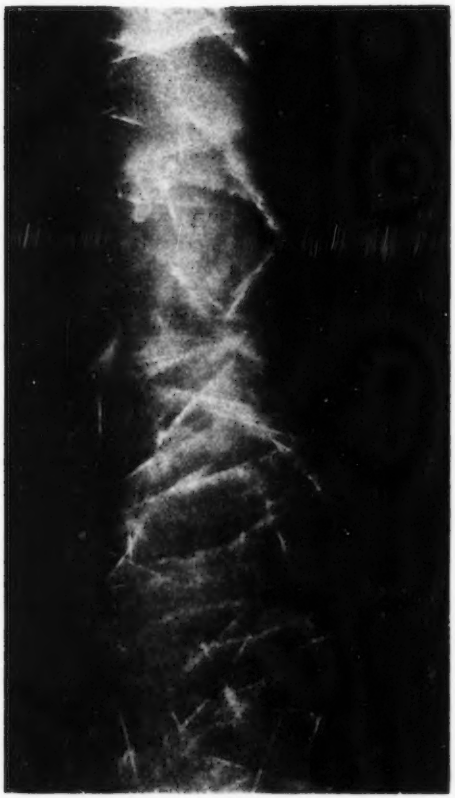

FIG. 4

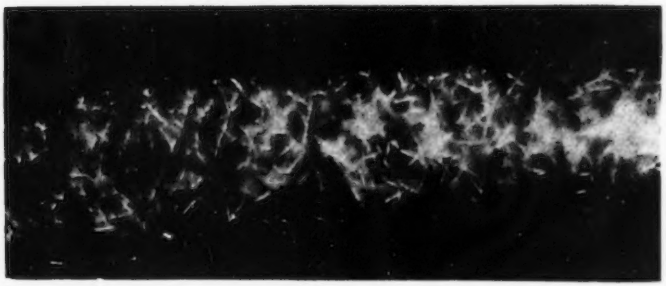

FIG. 5

Figs. 4 and 5. Figure 4, oxalated plasma of cat's blood clotted with thrombin. Magnification 512. To show the large needles obtained in slow clotting Figure 5, fibrinogen solution made from horse's plasma and clotted with thrombin. Magnification 512. To show less complete formation of needles.